The American Journal of Cardiology®

MARCH 1, 1991

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240 TOTAL

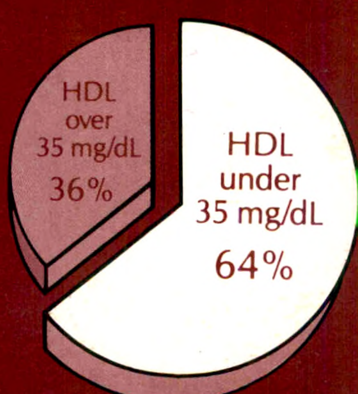
<35 HDL

Low HDL with elevated LDL and triglycerides:

A common denominator of many heart attack victims

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (< 35 mg/dL) baseline level of HDL cholesterol.[2] LOPID® (gemfibrozil) is not indicated for the treatment of patients with low HDL cholesterol as their only lipid abnormality.

HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



PARKE-DAVIS

The American Journal of Cardiology®

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Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 3 times a month in January, April and December, 2 times in February, March, July and August, 4 times in May, June and November, and 5 times in September and October, by Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Robert T. Brawn, Senior Vice President/General Manager; Jerry D. Neth, Senior Vice President/Publishing Operations; J.J. Walsh, Senior Vice President/Finance; Thomas J. Dellamaria, Senior Vice President/Production and Manufacturing. Executive, Editorial and Advertising Offices: 249 West 17th Street, New York, NY 10011. Printed in Easton, PA.
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Circulation records are maintained at 44 Cook Street, Denver, CO 80206. Second class postage paid at Denver, CO, and at additional mailing office. Printed in USA Trademark™ in US Patent Office.

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MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor in Chief, The American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814. See "Instructions to Authors," page 540.
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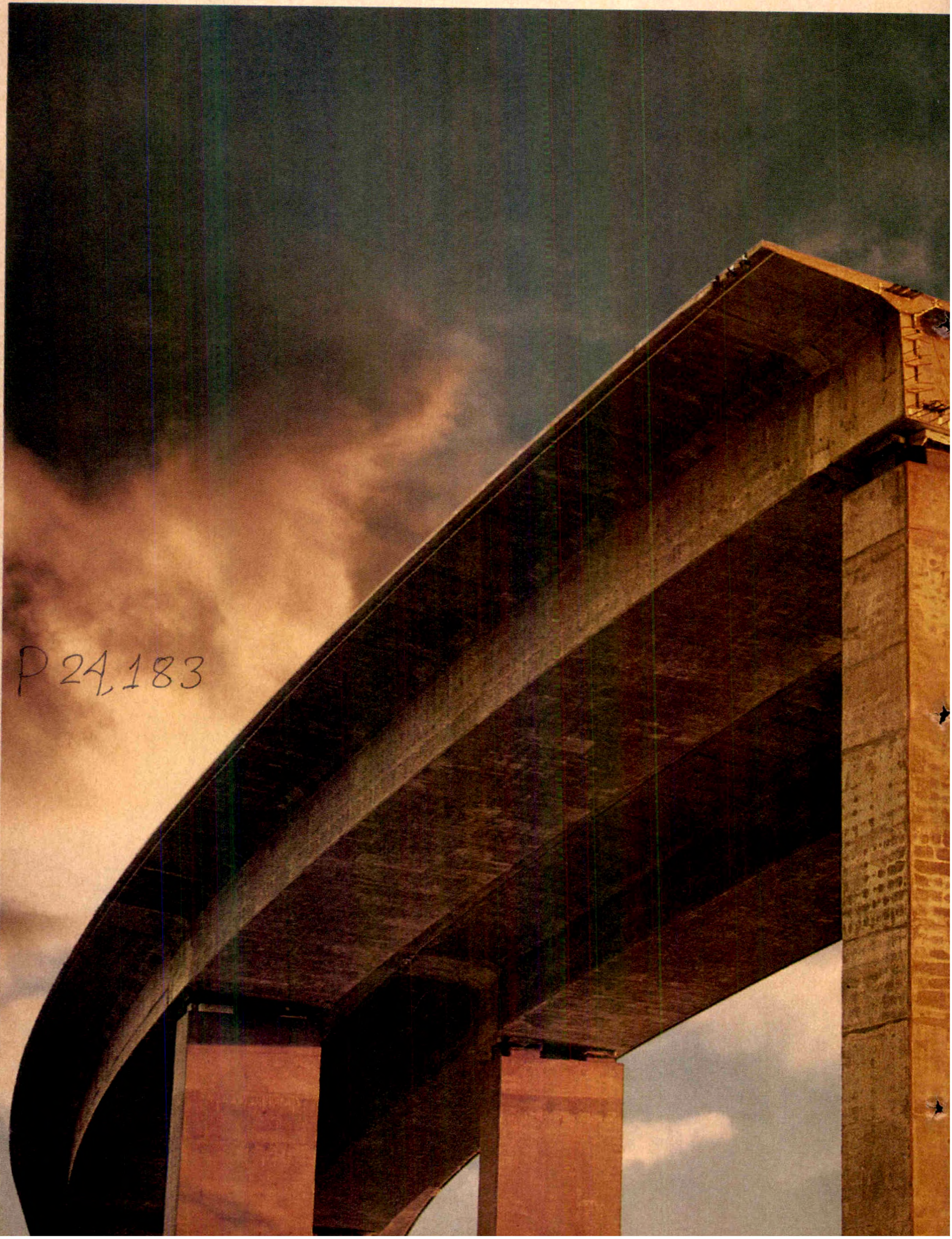
In cardiac imaging, the failure to
can lead you down an expensi



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Frequency of Success and Complications of Coronary Angioplasty of a Stenosis at the Ostium of a Branch Vessel

David W. Mathias, Jodi Fishman Mooney, Helmut W. Lange, Irvin F. Goldenberg, Fredarick L. Gobel, and Michael R. Mooney

One hundred six patients with coronary angioplasty of 119 stenoses located at the ostium of a coronary branch vessel were evaluated for technical success and in-hospital complications, and compared with the general angioplasty population. Angioplasty of ostial branch stenoses results in decreased procedural success and significant residual stenosis despite adequate balloon sizing, suggesting arterial elastic recoil and a significant increase in complications.

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Pericardial Effusion After Intravenous Recombinant Tissue-Type Plasminogen Activator for Acute Myocardial Infarction

Robert N. Belkin, Daniel B. Mark, Lynn Aronson, Hanna Szwed, Robert M. Califf, and Joseph Kisslo

To determine the frequency and clinical sequelae of pericardial effusion in patients with acute myocardial infarction treated with thrombolytic therapy, 52 patients who underwent serial echocardiography during the first Thrombolysis and Angioplasty in Myocardial Infarction trial were studied prospectively. No patient developed cardiac tamponade, the prevalence of pericardial effusion appeared similar to that in more conservatively treated patients, and adverse sequelae were rare.

501

Comparison of the Efficacy of Questran Light, a New Formulation of Cholestyramine Powder, to Regular Questran in Maintaining Lowered Plasma Cholesterol Levels

William Insull, Jr., Norman R. Marquis, and Michael C. Tsianco

Sixty-one men with known hypercholesterolemia were chosen to test the effectiveness of the new formulation Questran Light against the proven effectiveness of the currently marketed Questran in maintaining reduced plasma cholesterol levels. There were no statistically significant mean changes from baseline to end-point lipid/lipoprotein levels in the 2 groups taking Questran Light and regular Questran. The new low-calorie cholestyramine formulation appears to be equally effective in maintaining lowered plasma cholesterol levels as the current regular formulation.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Characteristics of Accessory Pathways Exhibiting Decremental Conduction

Challon J. Murdock, James W. Leitch, Wee Siong Teo, Arjun D. Sharma, Raymond Yee, and George J. Klein

The authors examined the prevalence, electrophysiologic characteristics and functional significance of decremental conduction over an accessory pathway in a retrospective study of 653 patients. Data demonstrate that decremental conduction over accessory pathways is uncommon. Anterograde decremental conduction usually occurs in right-sided or septal pathways that often do not conduct in retrograde direction.

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Usefulness of d, l Sotalol for Suppression of Chronic Ventricular Arrhythmias

Maria I. Anastasiou-Nana, Edward M. Gilbert, Ronald H. Miller, Steven Singh, Roger A. Freedman, Deborah L. Keefe, Sanjeev Saksena, Daniel J. MacNeil, and Jeffrey L. Anderson

To determine the efficacy and safety of sotalol, a β-blocking drug with class III antiarrhythmic activity, 114 patients with chronically ≥ 30 ventricular premature complexes per hour were randomized to high ($n = 39$) or low ($n = 38$) divided doses (640 and 320 mg/day, respectively) or to placebo ($n = 37$) in this 6-week, double-blind, multicenter trial. Sotalol works efficaciously in suppressing VPCs, and is somewhat less effective but more tolerable in low doses.

VALVULAR HEART DISEASE

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Doppler Echocardiographic Comparison of the Carpentier and Duran Anuloplasty Rings Versus No Ring After Mitral Valve Repair for Mitral Regurgitation

Brigitte Unger-Graeber, Richard T. Lee, Martin St. John Sutton, Maureen Plappert, John J. Collins, and Lawrence H. Cohn

The authors compared the hemodynamic results of different anuloplasty techniques of primary valve repair for mitral regurgitation in 122 patients who underwent Doppler echocardiography 5 to 10 days after operation. Data suggest that Carpentier and Duran rings decrease the hemodynamic mitral valve area; however, the decrease in valve area is small and not associated with a clinically important increase in transvalvular gradient.

MISCELLANEOUS

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Influence of Sympathetic Stimulation and Parasympathetic Withdrawal on Doppler Echocardiographic Left Ventricular Diastolic Filling Velocities in Young Normal Subjects

Karl-Arne Johannessen, Manuel Cerqueira, Richard C. Veith, and John R. Stratton

The effects of atropine and epinephrine on diastolic mitral filling velocities were studied in 10 young normal subjects. Parasympathetic withdrawal reduces early filling velocities, increases atrial filling velocities and reduces the E/A ratio. In contrast, epinephrine at physiologic levels increases E, A and the E/A diastolic filling period. These findings document the importance of controlling for these factors if Doppler filling velocities are used to study diastolic function.

BRIEF REPORTS

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Effects of Aminophylline on Atrioventricular Conduction in Patients with Late Atrioventricular Block During Inferior Wall Acute Myocardial Infarction

Boris Strasberg, Rony Bassevich, Aviv Mager, Jairo Kusniec, Alex Sagie, and Samuel Sclarovsky

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CORONARY ARTERY DISEASE

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Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results II. Assessment of the Human Lens After 48 Weeks of Treatment with Lovastatin

Alan M. Laties, Charles L. Shear, Erik A. Lippa, A. Lawrence Gould, Hugh R. Taylor, Dennis P. Hurley, Wendy P. Stephenson, Edwin U. Keates, Mary Ann Tupy-Visich, and Athanassios N. Chremos

The crystalline lenses of hypercholesterolemic patients were assessed before and after 48 weeks of treatment with lovastatin or placebo to determine the effect of lovastatin on the human lens. Patients were given a biomicroscopic (slit-lamp) examination of the lens, and a previously validated, standardized classification system was used to describe the findings. A total of 8,245 patients were randomly assigned in equal numbers to treatment with placebo or lovastatin 20 or 40 mg once daily, and 20 or 40 mg twice daily, in this double-blind, parallel-group study. Analyses of the week 48 distributions of cortical, nuclear and subcapsular opacities, and visual acuity assessments showed no statistically significant differences ($p < 0.01$) between the placebo and lovastatin treatment groups. Moreover, no significant differences were found among the groups in the frequencies of spontaneously reported adverse ophthalmologic experiences. No evidence was found for an effect of lovastatin on the human lens after 48 weeks of treatment.

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Effect of Left Ventricular Aneurysm on Risk of Sudden and Nonsudden Cardiac Death

Constantine A. Hassapoyannes, Leslie M. Stuck, Carlton A. Hornung, Michael C. Berbin, and Nancy C. Flowers

To determine the effect of left ventricular (LV) aneurysm on the risk of late sudden and nonsudden cardiac death, we studied 121 patients with healed myocardial infarction (MI) [55 manifesting akinesia on ventriculography (MI group) and 66 with diastolic deformity (eccentricity) and systolic dyskinesia (LV aneurysm group)] over a 5.7-year interval. Ventricular ectopy was quantitated by 24-hour Holter monitoring. For all patients, ejection fraction was the best predictor of total cardiac death ($p < 0.005$), and LV aneurysm the best predictor of sudden cardiac death ($p < 0.05$). In the LV aneurysm group, total cardiac death was predicted by decreasing ejection fraction ($p < 0.05$), ventricular tachycardia ($p < 0.01$)

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and right coronary disease (p <0.1). Ventricular tachycardia was the sole predictor of sudden cardiac death (p <0.05). Risk of late sudden cardiac death is small after uncomplicated MI, but significant in the presence of aneurysm.

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Angiographic Morphology in Unstable Angina and Its Relation to Transient Myocardial Ischemia and Hospital Outcome

Raffaele Bugiardini, Andrea Pozzati, Alberico Borghi, Gian Luigi Morgagni, Filippo Ottani, Antongiulio Muzi, and Paolo Puddu

Complex stenosis morphology frequently occurs in patients with unstable angina. However, its prognostic significance is still uncertain. Accordingly, early coronary angiography was performed in 88 patients presenting with unstable angina. Continuous electrocardiographic recordings were made during the first 24 hours. Over the subsequent month, 32 of 58 patients presenting with complex stenosis morphology had a major coronary event (sudden death, myocardial infarction or emergency revascularization). Of these 32 patients, 29 had a cumulative transient myocardial ischemia duration of ≥60 minutes per 24 hours. Only 2 patients, who had smooth, regular stenoses, had an unfavorable outcome. It is concluded that plaque disruption is a potential trigger for rapidly progressing unstable angina. Ultimate prognosis, however, depends on the association of this finding with other precipitating factors that underlie the degree of coronary stenosis and related ischemia. Association of complex coronary morphology with sustained myocardial ischemia may identify the majority of patients (85%) who later have adverse coronary events.

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Anginal Symptoms Without Ischemic Electrocardiographic Changes During Ambulatory Monitoring in Men With Coronary Artery Disease

Dirk Hausmann, Peter Nikutta, Werner G. Daniel, Paul Wenzlaff, and Paul R. Lichtlen

The incidence of episodes of angina pectoris without electrocardiographic (ECG) signs of myocardial ischemia during 24-hour ambulatory monitoring was studied in 128 patients with stable angina pectoris, proven coronary artery disease and positive exercise test results: 104 episodes occurred only with angina pectoris, 86 episodes occurred with both ECG changes and angina pectoris, and 255 episodes occurred only with ECG changes. Anginal episodes without ECG changes were detected in 44 patients (group A); in this group, 15 patients had both angina pectoris without ECG changes and episodes with ischemic ECG changes. In 84 patients (group B) all episodes were accompanied by ischemic ECG changes. Patients in groups A and B had no differences in the extent of coronary artery disease and in exercise test data; however, maximal ST-segment depression during exercise testing was significantly greater in group B than in group A patients. Anginal episodes without ECG changes in patients also having episodes with ECG changes during the same recording period most probably are of ischemic origin and should be included when estimating the extent of myocardial ischemia.

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sis and Angioplasty in Myocardial Infarction trial at Duke University Medical Center. Pericardial effusion was present in 8% of patients at day 0, in 5% at day 1, in 19% at day 3 and in 24% at day 6. By day 6, 3 of 10 effusions were moderate and 1 was large. No patient developed tamponade. Thus, the prevalence of pericardial effusion after thrombolytic therapy appears similar to that in more conservatively treated patients, and adverse sequelae are rare.

501

Comparison of the Efficacy of Questran Light, a New Formulation of Cholestyramine Powder, to Regular Questran in Maintaining Lowered Plasma Cholesterol Levels

William Insull, Jr., Norman R. Marquis, and Michael C. Tsianco

The efficacy of Questran Light, a new low-calorie formulation of cholestyramine, was tested against the proven effectiveness of the currently marketed formulation of Questran. Participants included 61 men with known hypercholesterolemia who were treated with 24 g of regular Questran in 2 divided doses daily for 3 weeks to establish a baseline of reduced plasma low-density lipoprotein cholesterol and randomized into 2 groups for 4 test weeks. One group received 24 g of cholestyramine of the Questran Light formulation and the other continued to take regular Questran with average adherence during the test period of 91 and 93%, respectively. There were no statistically significant mean changes from baseline to end-point lipid/lipoprotein levels in the 2 groups. The new low-calorie cholestyramine formulation appears to be equally effective in maintaining lowered plasma cholesterol levels as the currently marketed formulation.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

506

Characteristics of Accessory Pathways Exhibiting Decremental Conduction

Challon J. Murdock, James W. Leitch, Wee Siong Teo, Arjun D. Sharma, Raymond Yee, and George J. Klein

This study examined the prevalence, electrophysiologic characteristics and functional significance of decremental conduction over an accessory pathway. Decremental conduction was identified in 50 of 653 patients with an accessory pathway demonstrated at electrophysiologic study (7.6%). Anterograde decremental pathways were usually right-sided or septal and often did not conduct in the retrograde direction. There was no significant difference in the effective refractory period or shortest cycle length with 1:1 conduction over decremental accessory pathways in anterograde and retrograde directions. The shortest RR interval in atrial fibrillation between 2 preexcited QRS complexes was longer in patients with anterograde decremental conduction than in patients with accessory pathways without decremental conduction.

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Usefulness of d, l Sotalol for Suppression of Chronic Ventricular Arrhythmias

Maria I. Anastasiou-Nana, Edward M. Gilbert, Ronald H. Miller, Steven Singh, Roger A. Freedman, Deborah L. Keefe, Sanjeev Saksena, Daniel J. MacNeil, and Jeffrey L. Anderson

The antiarrhythmic efficacy and safety of 2 doses of sotalol (320 and 640 mg/day in 2 divided doses) were compared to placebo in this 6-week randomized, double-blind, multicenter study of 114 patients with ≥ 30 ventricular premature complexes (VPCs) per hour. Total VPCs were reduced 10% by placebo ($n = 37$), 75% by low-dose ($n = 38$; $p < 0.001$ vs placebo) and 88% by high-dose sotalol ($n = 39$; $p < 0.001$ vs placebo; $p < 0.05$ vs low dose). VPC reductions of $\geq 75\%$ were achieved in 6, 34 and 71% of patients, respectively ($p < 0.003$, sotalol vs placebo; $p = 0.007$, high vs low dose). Repetitive VPCs were suppressed 25% by placebo (difference not significant), 80% by low-dose ($p < 0.003$) and 78% by high-dose sotalol ($p < 0.005$). Sotalol increased PR and corrected JT intervals and reduced heart rate. Proarrhythmia (nonfatal) occurred in 3 sotalol and 2 placebo patients. Adverse effects were generally mild but dose-related. Sotalol is an effective antiarrhythmic drug; a lower dose is somewhat less effective in reducing VPC rates but is better tolerated.

VALVULAR HEART DISEASE

517

Doppler Echocardiographic Comparison of the Carpentier and Duran Anuloplasty Rings Versus No Ring After Mitral Valve Repair for Mitral Regurgitation

Brigitte Unger-Graeber, Richard T. Lee, Martin St. John Sutton, Maureen Plappert, John J. Collins, and Lawrence H. Cohn

To compare the hemodynamic results of different anuloplasty techniques of primary valve repair for mitral regurgitation, 122 patients were prospectively studied with Doppler echocardiograms 5 to 10 days postoperatively. Forty-eight patients received the flexible Duran ring, 46 received the more rigid Carpentier ring, and 28 patients received no ring. Doppler echocardiography demonstrated a significant decrease in mitral valve area estimated by the pressure half-time method in patients who received either a Carpentier (2.6 ± 0.8 cm^2) or Duran ring (2.8 ± 0.8 cm^2) when compared with patients who received no ring (3.2 ± 0.7 cm^2) ($p = 0.01$). These data suggest that Carpentier and Duran rings decrease the hemodynamic mitral valve area; however, the decrease in valve area is small and not associated with a clinically important increase in transvalvular gradient.

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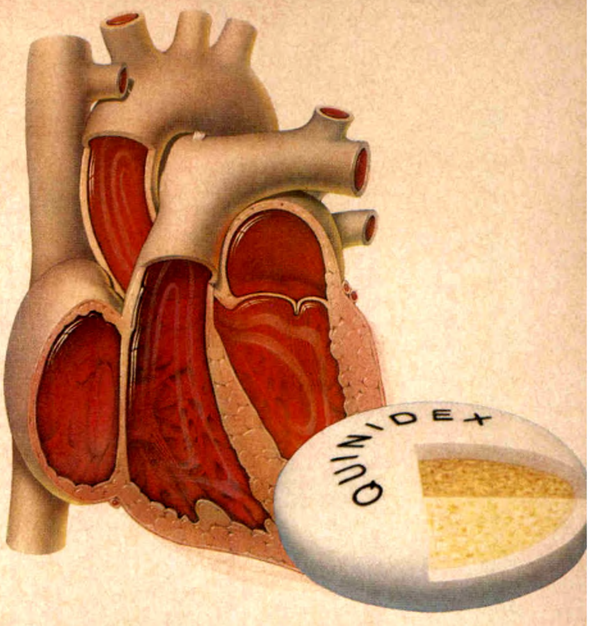

B.I.D.

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	**Effect**
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital), phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

Twice-a-day dosing* to make life easier for your arrhythmia patients. That's the Quinidex® advantage. Because, like the heart, Quinidex Extentabs® have been uniquely constructed for dependable around-the-clock performance.

Some patients may require t.i.d. dosing.

QUINIDEX
EXTENTABS
(Quinidine Sulfate Extended release Tablets, USP) 300 mg

A·H·ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-660

MISCELLANEOUS

The effects of atropine and epinephrine on diastolic mitral filling velocities were studied in 10 young normal subjects. At the highest atropine dose, heart rate increased by 75%, the diastolic filling period decreased by 61%, the peak early (E) decreased 23%, the peak atrial (A) increased 103%, and the E/A ratio decreased by 60% (all p <0.001). Changes in the E, A and the E/A ratio were highly correlated to changes in the diastolic filling period. Effects of atropine on the E/A ratio were normalized by dividing by the diastolic filling period (E/A/diastolic filling period). At the highest infusion dose, epinephrine increased the heart rate by 26%, decreased the diastolic filling period by 22%, increased the E by 43%, and increased the A by 30% (all p <0.01). The E/A ratio increased 15% (p = 0.13), whereas the E/A/diastolic filling period increased by 43% (p <0.01). Increases in epinephrine levels directly correlated to increases in E peak, A peak and the E/A/diastolic filling period. These findings document the significant influences of parasympathetic withdrawal and sympathetic activation on diastolic mitral inflow velocities.

BRIEF REPORTS

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READERS' COMMENTS

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*CAPOTEN (captopril tablets) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

FROM THE EDITOR

INSTRUCTIONS TO AUTHORS on page 540

CLASSIFIED ADVERTISING on pages A56, A64, A68

kindhearted.

Kindhearted Lozol is not associated with adverse lipid changes* — unlike hydrochlorothiazide. In fact, both short- and long-term studies demonstrate that Lozol reduces hypertension without compromising cholesterol.[1–5] For patients at higher cardiovascular risk because of high blood pressure and lipid concerns, Kindhearted Lozol offers safe, effective diuretic therapy.

ONE A DAY

LOZOL®

INDAPAMIDE 2.5mg

The diuretic that doesn't compromise cholesterol

Please see brief summary of prescribing information below.

*Lozol is not a cholesterol-lowering agent, nor has it been shown to reduce existing atherosclerotic plaque.

LOZOL® (indapamide) **2.5 mg tablets**

BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with $\geq 5\%$ cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; $< 5\%$ cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: June 1990

References: 1. Horgan JH, O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response to indapamide. *Postgrad Med J* 1981;57(Suppl 2): 64–67. **2.** Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258–262. **3.** Weidmann P, Meier A, Mordasini R, et al: Diuretic treatment and serum lipoproteins: Effects of tienilic acid and indapamide. *Klin Wochenschr* 1981;59:343–346. **4.** Meyer-Sabellek W, Gotzen R, Heitz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(Suppl II):170–174. **5.** Scalabrino A, Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17–22.

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Printed in U.S.A.
LZ06291A 2/91 FC# 91-118

The American Journal of Cardiology

MARCH 1, 1991, VOL. 67, NO. 6

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results II. Assessment of the Human Lens After 48 Weeks of Treatment with Lovastatin

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The crystalline lenses of hypercholesterolemic patients were assessed before and after 48 weeks of treatment with lovastatin or placebo to determine the effect of lovastatin on the human lens. Patients were given a biomicroscopic (slit-lamp) examination of the lens, and a previously validated, standardized classification system was used to describe the findings. A total of 8,245 patients were randomly assigned in equal numbers to treatment with placebo or lovastatin 20 or 40 mg once or twice daily in this double-blind, parallel-group study. Statistical analyses of the distribution of cortical, nuclear and subcapsular opacities at 48 weeks, adjusted for age and presence of an opacity at baseline, showed no significant differences ($p < 0.01$) between the placebo and lovastatin-treated groups. Visual acuity assessments at week 48 were also not found to have significantly different distributions among treatment groups. Moreover, no significant differences were found among the groups in the frequencies of ≥2-line worsening in visual acuity with concurrent progression in lenticular opacity, cataract extraction, or any spontaneously reported adverse ophthalmologic experience. No evidence was found for an effect of lovastatin on the human lens after 48 weeks of treatment.

(Am J Cardiol 1991;67:447–453)

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Lovastatin is the first marketed drug of a new class of cholesterol-lowering compounds, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. These act by the reversible competitive inhibition of HMG-CoA reductase, a rate-limiting enzyme early in the pathway of cholesterol biosynthesis.[1] A marked reduction of plasma low-density lipoprotein cholesterol, modest decrease in triglycerides, and a modest increase in high-density lipoprotein cholesterol are observed.[2–5] Lovastatin is currently used in the treatment of primary hypercholesterolemia.[6–8]

At 40 to 60 times the maximum recommended human dose, lovastatin has been shown to cause subcapsular opacities, predominately posterior, in beagle dogs.[9] The mechanism for this occurrence is not clearly understood. In early clinical trials, ascertainment of a possible drug effect was limited by both the lack of a placebo control in the follow-up of patients and the lack of standardization of the methods used to report findings from the slit-lamp examination. The package circular for lovastatin recommends that patients treated with lovastatin be given a biomicroscopic examination of the lens before or shortly after initiation of treatment and annually thereafter.*

We report here the ophthalmologic findings from a 362-center, randomized, double-blind, placebo-controlled, parallel-group, 48-week study conducted to assess the long-term efficacy and safety profile of lovastatin. In all, 8,245 patients with moderate primary hypercholesterolemia were randomized to treatment. Patients were given a biomicroscopic (slit-lamp) examination of the lens, and findings were standardized using a previously tested system. The results show no evidence of an effect of lovastatin on the human crystalline lens after 48 weeks of treatment.

METHODS

The study design and general comparability of treatment groups at baseline have been reported in detail elsewhere[10] and are summarized here.

*Mevacor® package insert, Merck & Co., Inc., June 1989.

Patient selection: Patients 18 to 70 years old with moderate primary hypercholesterolemia were eligible for participation. Lipid and lipoprotein criteria for entry were plasma total cholesterol from 240 to 300 mg/dl, low-density lipoprotein cholesterol $\geq$160 mg/dl and triglycerides <350 mg/dl. Patients were excluded if they were women with childbearing potential, if they had impaired hepatic or renal function, unstable medical conditions, or diabetes mellitus requiring insulin or oral hypoglycemic agents. The presence of coronary artery disease risk factors or of chronic ophthalmologic conditions did not exclude patients from participation.

The study protocol was approved by the institutional review board at each participating site, and patients gave written informed consent before participating in the trial.

General design: After a minimum of 4 to 6 weeks on a lipid-lowering diet (American Heart Association Step I or more stringent), patients fulfilling the qualifying criteria of the study were randomly assigned to 1 of 5 parallel treatment groups: placebo or lovastatin 20 or 40 mg once or twice daily. Patients, investigators, ophthalmologists and study staff were blinded to treatment group. Patients then continued their lipid-lowering diet and took the assigned study medication for 48 weeks, with return visits every 6 weeks for clinical and laboratory assessments, including the reporting of any adverse experiences. Investigators and patients were blinded to the results of lipid assessments. Ophthalmologic examinations were performed at baseline and weeks 24 and 48 of the study by ophthalmologists assigned by the individual study site. Investigators from 362 clinical sites in the continental United States participated in this multicenter study.

Ophthalmologic examination: Each ophthalmologic examination included the assessment of best-corrected Snellen visual acuity at distance, examination of the lens with slit-lamp after dilation of the pupil to $\geq$6 mm, and external and anterior segment examination and ophthalmoscopic evaluation of the retina. Whenever possible, the same ophthalmologist was to perform all of a patient's study examinations. This, in fact, occurred for 87% of the patients in each treatment group. The ophthalmologist was instructed not to refer to observations from past examinations of a patient when completing observations during an examination.

To standardize the recording of lens findings during the examinations, observations were graded for severity within each of 7 categories: (1) cortical wedges and spokes-quadrants affected (0,1,2,3,4); (2) cortical wedges and spokes-maximal inward extent (minimal, moderate, advanced); (3) cortical waterclefts, vacuoles and flakes (none, few, moderate, many); (4) nuclear opacity (absent, trace, moderate, dense); (5) nuclear coloration (no color, pale yellow, yellow, yellow/brown); (6) posterior subcapsular opacity (absent, just visible, minimal, moderate, advanced); and (7) anterior subcapsular opacity (same grades as category 6). This classification draws heavily on methods devised by Taylor and West[11] and is comparable to those devised by others.[12,13] Ophthalmologists were provided with written instructions together with photographic standards and sketches depicting each grade in the 7 categories. Reliability testing of the classification system has shown acceptable intraexaminer reliability for the classes of lens findings of greatest interest: cortical wedges and spokes-quadrants affected, nuclear opacity, and posterior subcapsular opacity.[14]

Statistical analysis: The effect of lovastatin on the human lens was assessed using findings from the lens examinations, visual acuity assessments and reports of ophthalmologic adverse experiences volunteered by the patients.

The frequency distributions of the grades from the lens examinations and of the visual acuity assessments after 48 weeks of treatment were compared among the treatment groups; adjustments were made for age group and the presence versus absence of a finding (for lens opacities) or 20/20 versus worse vision (for visual acuity) at baseline.[15] These adjustments were made to increase the sensitivity of the comparisons among treatment groups. Differences among treatment groups in the adjusted frequency distributions were used to estimate drug effects; the following comparisons were made: (1) lovastatin 40 mg twice daily versus placebo, (2) lovastatin 40 mg daily (20 mg twice and 40 mg once daily combined) versus placebo, (3) lovastatin 40 mg twice daily versus lovastatin 20 mg once daily, and (4) lovastatin 20 mg twice daily versus lovastatin 40 mg once daily. These comparisons correspond to hypotheses identified at the outset: comparisons 1 and 2 address treatment effects relative to placebo, comparison 3 tests for a dose-response relation, and comparison 4 addresses the possibility of a regimen effect. Separate analyses were performed for the right and left eye results to confirm possibly significant findings, since any toxic effect of a systemic agent should occur in both eyes. In all, 64 comparisons were made (7 lens categories + visual acuity) × (4 treatment comparisons) × (2 eyes). To minimize the possibility of obtaining artifactual differences arising from multiple comparisons and the large sample size, a computed significance level of $p < 0.01$ was used to reject the hypothesis that the true value of each comparison was zero.

To ensure that the results would reflect outcomes after a reasonable duration of treatment, the analyses included only data on patients with an examination after $\geq$270 days with treatment (range 270 to 535 days, median = 339). The findings for the patients omitted from the analyses were also examined, and the results were similar.

Owing to the volume of results and the similarity of outcome in all parameters, detailed tabulations are presented only for the categories of greatest interest: cortical wedges and spokes (quadrants affected), nuclear opacity, posterior subcapsular opacity and visual acuity. Statistically significant findings were not found in either eye for the lens opacity categories not presented here.

A total of 8,245 patients were randomized to treatment (placebo = 1,663; 20 mg once daily = 1,642; 40 mg once daily = 1,645; 20 mg twice daily = 1,646; 40 mg twice daily = 1,649). Of these, patients were not

TABLE I General Characteristics of Patients at Baseline

		Treatment Group—Lovastatin			
	Placebo	20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Patients randomized	1,663	1,642	1,645	1,646	1,649
Sex (percent male)	58	60	59	58	59
Age (mean years)					
Men	54	54	54	55	54
Women	59	58	59	59	58
Ethnicity (percent white)	92	91	93	91	91
Lipid/lipoprotein levels (mg/dl)					
Total cholesterol (mean)	257	258	258	259	258
LDL cholesterol (mean)	179	180	180	181	180
HDL cholesterol (mean)	45	45	45	45	45
Triglycerides (median)	156	152	156	157	154
Percent of Total					
Hypertensive	41	41	38	40	38
Current cigarette smokers	18	20	18	18	18
History of coronary artery disease	29	29	27	29	28

bid = twice daily; qpm = once daily.

TABLE II Ophthalmologic Characteristics of Patients at Baseline, Right Eye*

		Treatment Group—Lovastatin			
	Placebo	20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
	Percent of Total				
History					
Cataract extraction	2	2	1	2	1
Exposure to glucocorticoids (>4 months' duration)	2	1	2	2	2
Glaucoma	3	3	3	3	3
Ocular surgery/laser therapy	3	3	3	3	3
Visual acuity					
20/25 to 20/40	21	22	20	22	23
20/50 or worse	3	2	2	2	2
Slit-lamp examination†					
Cortical opacity					
Waterclefts/vacuoles/flakes	29	27	29	31	27
Wedges/spokes	15	16	14	17	16
Nuclear Finding					
Opacity	41	40	39	40	38
Coloration	43	43	42	44	40
Subcapsular opacity					
Posterior	8	8	8	8	9
Anterior	2	4	3	3	3

* Similar results for left eye.
† Percentage reported is for the presence of any opacification.
bid = twice daily; qpm = once daily.

included in the visual acuity and lens opacities analyses if any of the following conditions applied to them (numbers are the range of patients excluded for right or left eye analyses): absence of baseline examination or value not recorded (4 to 15); aphakia, pseudophakia or cataract extraction recorded at baseline (19 to 35) or at any time after randomization (1 to 7) (the frequencies of the latter conditions were analyzed as adverse experiences and excluded here to remove artificial improvements over time); absence of follow-up examination or value not recorded after day 269 (249 to 298). Follow-up slit-lamp examination and visual acuity assessments before day 270 were available in 55 to 63% of patients (in each treatment group) who withdrew before the study completion, and inspection of these patients' outcomes showed no material differences by treatment group. With these exclusions, from 79 to 82% of randomized patients in each treatment group were included in the analyses of visual acuity and lens opacities.

Ophthalmologic adverse experiences were defined as signs and symptoms reported by the patient at any time during the trial that indicated possible ocular deterioration, regardless of suspected cause.[16] The usual 2×2 chi-square statistic was used to test for between-group differences in incidence of ophthalmologic adverse experiences. This analysis included all patients randomized to treatment, regardless of how long they remained in the study.

RESULTS

Effectiveness of randomization: The treatment groups were similar at baseline in the distributions of nonophthalmologic (Table I) and ophthalmologic (Table II) characteristics. A total of 8,245 patients were randomized to study medication, and 59% were men. The prevalence of opacities at baseline (right eye) ranged from 3% for anterior subcapsular opacification to 42% for nuclear coloration (Table II). More than half the patients with an opacity present at baseline were scored in the lowest grade. For example, 56% of patients with cortical wedges and spokes had only 1 quadrant affected; 65% of patients with nuclear opacities had opacities graded as "trace"; and 64% of patients with posterior subcapsular opacities had opacities graded as "just visible."

The distributions of lens findings and visual acuity assessments at baseline were consistently and directly related to age in the same way for all treatment groups. Overall, 5% of the patients <45 years of age had cortical wedges and spokes present, compared with 25% of the patients >64 years of age. The corresponding percentages were 10 vs 61% for nuclear opacity, and 4 vs 12% for posterior subcapsular opacity.

Study participation: Overall, 6,847 patients (83%) completed the study, ranging from 82% (40 mg once daily) to 85% (20 mg twice daily) of the patients in each treatment group (Table III). Ophthalmologic adverse experiences were cited as the primary reason for withdrawal at similar rates in the placebo and lovastatin treatment groups (0.6 to 0.8%). Loss to follow-up was equally distributed among all treatment groups (2 to 3%).

Lens examination outcomes: The distribution of findings from the lens examinations at week 48 are provided for cortical wedges and spokes by number of quadrants affected (Table IV), nuclear opacity (Table V), and posterior subcapsular opacity (Tables VI and VII). Results are presented separately for the patients

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TABLE III Status of Patients During Study Participation

	Placebo	Treatment Group—Lovastatin 20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
	Number (percent of total)				
Completed 48 weeks	1370 (82)	1370 (83)	1352 (82)	1394 (85)	1361 (83)
Lost to follow-up	49 (3)	39 (2)	50 (3)	34 (2)	42 (3)
Withdrawn*	244 (15)	233 (14)	243 (15)	218 (13)	246 (15)
Due to ophthalmologic adverse experience†	11 (1)	11 (1)	13 (1)	10 (1)	11 (1)

* Includes clinical or laboratory adverse experiences, protocol deviation, patient choice, and all other reasons.
† This is a subcategory of withdrawals and should not be summed with other categories.
bid = twice daily; qpm = once daily.

TABLE IV Distribution of Cortical Wedges and Spokes, Number of Quadrants Affected, Right Eye at Week 48*

Quadrants Affected at Week 48	Placebo	Treatment Group—Lovastatin 20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Patients with No Quadrants Affected at Baseline					
0	1,076 (95.4)	1,064 (94.7)	1,085 (95.4)	1,044 (93.9)	1,072 (94.8)
1	25 (2.2)	44 (3.9)	34 (3.0)	52 (4.7)	44 (3.9)
2	11 (1.0)	8 (0.7)	10 (0.9)	7 (0.6)	11 (1.0)
3	3 (0.3)	4 (0.4)	4 (0.4)	0	2 (0.2)
4	13 (1.2)	3 (0.3)	4 (0.4)	9 (0.8)	2 (0.2)
Patients with Any Quadrants Affected at Baseline					
0	42 (21.6)	50 (22.9)	34 (17.8)	38 (16.5)	39 (18.9)
1	79 (40.7)	83 (38.1)	83 (43.5)	99 (42.9)	75 (36.4)
2	37 (19.1)	38 (17.4)	38 (19.9)	47 (20.3)	55 (26.7)
3	10 (5.2)	18 (8.3)	11 (5.8)	22 (9.5)	11 (5.3)
4	26 (13.4)	29 (13.3)	25 (13.1)	25 (10.8)	26 (12.6)

* Patients with cataract extraction or aphakia are omitted. Numbers are patient counts with percentage in parentheses. Results for left eye were similar. No significant differences (p <0.05) were found in the distributions at week 48 for placebo- and lovastatin-treated groups.
bid = twice daily; qpm = once daily.

TABLE V Distribution of Nuclear Opacity, Right Eye at Week 48*

Nuclear Opacity at Week 48	Placebo	Treatment Group—Lovastatin 20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Patients with No Nuclear Opacity at Baseline					
Absent	706 (90.5)	705 (88.1)	694 (87.4)	710 (88.2)	745 (88.9)
Trace	74 (9.5)	93 (11.6)	96 (12.1)	94 (11.7)	87 (10.4)
Moderate	0	2 (0.3)	4 (0.5)	1 (0.1)	6 (0.7)
Advanced	0	0	0	0	0
Patients with Any Nuclear Opacity at Baseline					
Absent	84 (15.5)	90 (16.6)	73 (13.6)	66 (12.2)	69 (13.8)
Trace	380 (70.0)	395 (72.7)	395 (73.8)	397 (73.7)	375 (75.0)
Moderate	75 (13.8)	56 (10.3)	63 (11.8)	76 (14.1)	55 (11.0)
Advanced	4 (0.7)	2 (0.4)	4 (0.7)	0	1 (0.2)

* Patients with cataract extraction or aphakia are omitted. Numbers are patient counts with percentage in parentheses. Results for left eye were similar. No significant differences (p <0.05) were found in the distributions at week 48 for placebo and lovastatin treatment groups.
bid = twice daily; qpm = once daily.

with and without an opacity at baseline. The results for the cortex and nucleus are given for the right eye; the results for the left eye were similar. The results for posterior subcapsular opacity are given for both eyes because of slight differences in baseline distribution and because of the previous animal findings.

There were no statistically significant (p <0.01) differences among the treatment groups with respect to the distribution of right or left eye findings in any of the 7 lens opacity categories. In fact, none of the differences among the treatment groups even reached the 5% level of significance.

Inspection of these distributions revealed similar patterns for the different categories of opacity. For patients with no opacity at baseline, approximately 90% had no opacity at week 48; the remaining patients were distributed similarly by opacity grade among the placebo and lovastatin treatment groups. For patients with an opacity at baseline, from 12% (nuclear opacity) to 30% (posterior subcapsular opacity) were graded with no opacity at week 48, whereas the remaining patients were distributed similarly by opacity grade among the placebo and lovastatin treatment groups. The proportion of patients with an opacity at baseline but none at week 48 reflects misclassification in the rating system.

Visual acuity outcomes: Visual acuity results are summarized in Table VIII. About 75% of patients in all treatment groups had 20/20 vision at week 48, with an additional 20% assessed at 20/30. For the right eye findings at week 48, the difference in the distribution of visual acuity between the 20 mg twice daily and 40 mg once daily dosage groups neared significance (p =

TABLE VI Distribution of Posterior Subcapsular Opacity, Right Eye at Week 48*

Posterior Subcapsular Opacity at Week 48	Placebo	Treatment Group—Lovastatin 20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Patients with No Posterior Subcapsular Opacity at Baseline					
Absent	1,172	1,202	1,193	1,193	1,182
	(96.8)	(97.6)	(97.0)	(96.0)	(96.4)
Just visible	32	25	31	38	40
	(2.6)	(2.0)	(2.5)	(3.1)	(3.3)
Minimal	6	5	5	11	3
	(0.5)	(0.4)	(0.4)	(0.9)	(0.2)
Moderate	1	0	1	1	1
	(0.1)	(0.0)	(0.1)	(0.1)	(0.1)
Advanced	0	0	0	0	0
Patients with Any Posterior Subcapsular Opacity at Baseline					
Absent	31	27	30	23	31
	(27.4)	(24.3)	(30.0)	(23.0)	(27.4)
Just visible	45	49	43	46	46
	(39.8)	(44.1)	(43.0)	(46.0)	(40.7)
Minimal	28	17	16	21	22
	(24.8)	(15.3)	(16.0)	(21.0)	(19.5)
Moderate	6	15	11	9	11
	(5.3)	(13.5)	(11.0)	(9.0)	(9.7)
Advanced	3	3	0	1	3
	(2.7)	(2.7)		(1.0)	(2.7)

* Patients with cataract extraction or aphakia are omitted. Numbers are patient counts with percentage in parentheses. No significant differences ($p < 0.05$) were found in the distributions at week 48 for placebo and lovastatin-treated groups.
bid = twice daily; qpm = once daily.

TABLE VII Distribution of Posterior Subcapsular Opacity, Left Eye at Week 48*

Posterior Subcapsular Opacity at Week 48	Placebo	Treatment Group—Lovastatin 20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Patients with No Posterior Subcapsular Opacity at Baseline					
Absent	1,192	1,196	1,189	1,206	1,188
	(97.7)	(96.3)	(97.0)	(96.2)	(96.3)
Just visible	22	34	30	37	39
	(1.8)	(2.7)	(2.4)	(3.0)	(3.2)
Minimal	4	11	5	10	6
	(0.3)	(0.9)	(0.4)	(0.8)	(0.5)
Moderate	2	1	2	1	1
	(0.2)	(0.1)	(0.2)	(0.1)	(0.1)
Advanced	0	0	0	0	0
Patients with Any Posterior Subcapsular Opacity at Baseline					
Absent	29	30	29	22	27
	(27.9)	(27.8)	(29.0)	(23.7)	(25.7)
Just visible	44	47	49	43	41
	(42.3)	(43.5)	(49.0)	(46.2)	(39.0)
Minimal	22	19	13	18	20
	(21.2)	(17.6)	(13.0)	(19.4)	(19.0)
Moderate	7	11	8	9	16
	(6.7)	(10.2)	(8.0)	(9.7)	(15.2)
Advanced	2	1	1	1	1
	(1.9)	(0.9)	(1.0)	(1.1)	(1.0)

* Patients with cataract extraction or aphakia are omitted. Numbers are patient counts with percentage in parentheses. No significant differences ($p < 0.05$) were found in the distributions at week 48 for placebo and lovastatin-treated groups.
bid = twice daily; qpm = once daily.

0.015). The only other finding with a $p < 0.05$ was that the 40 mg twice daily group had better visual acuity (left eye) than the placebo group at week 48.

Adverse experiences: Ophthalmologic adverse experiences occurred with similar frequency among the treatment groups (Table IX). In the placebo group, 7 patients underwent cataract extraction, whereas the frequency ranged from 2 to 11 in the lovastatin-treated groups with no apparent dose relation. A ≥2-line worsening in visual acuity with concurrent worsening in a lens opacity (an event that was used to monitor individual patient safety) occurred in 8 patients receiving placebo and in 4 to 6 patients in any lovastatin treatment group. Ophthalmologic adverse experiences were reported with nearly equal frequency in the placebo (20%) and lovastatin treatment groups (21 to 22%). The most common experiences were decreased visual acuity, eye irritation, tearing, eye pain, visual disturbances and visual loss.

DISCUSSION

No evidence was found to indicate an effect of lovastatin on the human crystalline lens after 48 weeks of treatment. Analyses of findings from lens examinations, visual acuity assessments and adverse experiences revealed no significant differences among the placebo and lovastatin treatment groups. The frequency of loss to follow-up was low (3%), similar among the treatment groups, and therefore unlikely to have obscured poten-

TABLE VIII Distribution of Visual Acuity at Week 48

Visual Acuity at Week 48	Placebo	Treatment Group—Lovastatin 20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Right Eye*					
20/20	999	1,037	1,020	1,055	1,008
	(75.3)	(78.0)	(76.7)	(78.3)	(75.2)
20/30	255	267	269	253	267
	(19.2)	(20.1)	(20.2)	(18.8)	(19.9)
20/40	27	19	16	19	32
	(2.0)	(1.4)	(1.2)	(1.4)	(2.4)
20/50	11	4	9	3	12
	(0.8)	(0.3)	(0.7)	(0.2)	(0.9)
20/60 or worse	34	16	16	18	22
	(2.6)	(1.2)	(1.2)	(1.3)	(1.6)
Left Eye†					
20/20	983	1,019	1,030	1,042	1,021
	(74.2)	(75.4)	(77.4)	(77.2)	(76.1)
20/30	275	288	245	260	260
	(20.8)	(21.3)	(18.4)	(19.3)	(19.4)
20/40	31	17	26	19	24
	(2.3)	(1.3)	(2.0)	(1.4)	(1.8)
20/50	7	5	7	8	12
	(0.5)	(0.4)	(0.5)	(0.6)	(0.9)
20/60 or worse	29	23	22	21	25
	(2.2)	(1.7)	(1.7)	(1.6)	(1.9)

* $p < 0.05$ for the differences in distributions at week 48 for the 40 qpm versus 20 bid comparison; all others not significant.
† $p < 0.05$ for the differences in distributions at week 48 for the placebo versus 40 bid comparison, with placebo having worse vision; all others not significant.
bid = twice daily; qpm = once daily.

TABLE IX Incidence of Ophthalmologic Events and Adverse Experiences

	Placebo	Treatment Group—Lovastatin			
		20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
	Number (percent of total)				
Cataract extraction	7 (0.4)	2 (0.1)	7 (0.4)	11 (0.7)	5 (0.3)
≥2-line decrease in visual acuity with opacity progression	8 (0.5)	6 (0.4)	4 (0.3)	6 (0.4)	6 (0.4)
Any ophthalmologic adverse experience	317 (19.7)	333 (20.8)	332 (20.8)	338 (21.0)	349 (21.7)

No significant differences ($p < 0.05$) were found in the incidence of adverse experiences for the placebo and lovastatin treatment groups.
bid = twice daily; qpm = once daily.

tial effects of lovastatin on the lens. Although these results cannot exclude a potential effect of lovastatin on the lens with treatment longer than 48 weeks, they clearly demonstrate the absence of an early effect. Furthermore, patients studied for an average 3.6 years of treatment with lovastatin have also not shown an effect on the lens.[17]

This study has important qualitative and quantitative strengths that distinguish it from previously reported clinical trials of lovastatin concerning the lens.[5-8] These strengths comprise the use of a standardized system of known reliability for observing, grading and recording lens opacities during examination[16]; a very large sample size for a prospective clinical trial (1,600+ patients per group with quite similar characteristics at baseline); and a concurrent parallel placebo group. All of these allowed for the reliable detection of effects of smaller magnitude and lower frequency than was possible in previous studies. Because of the large sample size and the multiplicity of comparisons, statistical significance for any comparison required a p value <0.01. However, for completeness and to emphasize the lack of any evidence of a treatment effect, findings from the 2 comparisons with a nominal p value ≤0.05 have also been presented. Both comparisons involved visual acuity, and neither suggested an adverse effect of lovastatin.

Whereas the classification system used in this study showed acceptable intraexaminer reliability for the major classes of opacity,[14] it was not free of misclassification. This was evident from the proportion of patients found to have an opacity at baseline but none at week 48. The great majority of these misclassifications are of 1 grade magnitude,[14] and a separate report[18] of the ≥2 grade changes found in this study also revealed no effect of lovastatin on the lens.

The prevalence of lens opacity is known to be strongly correlated with age and other host and environmental factors.[19-22] The effect of aging over the course of this study can be prdicted from the age-specific increase in the prevalence of lens findings at baseline that was observed in this study and others.[19]

In conclusion, the results of this study indicate that treatment with lovastatin for 48 weeks is not associated with detectable changes in the human crystalline lens. This multicenter study, which enrolled 8,245 patients and used a standardized and validated system to classify findings from biomicroscopic (slit-lamp) examinations, is the largest longitudinal study reported to date in the evaluation of the development and progression of lens opacity.

Acknowledgment: We gratefully acknowledge the 362 investigators and participating ophthalmologists, the co-investigators, study coordinators, and 8,245 patients who made this study possible. We are indebted to the staffs at Clinical Research International, Inc., Research Triangle Park, North Carolina, who implemented the study and served as the coordinating center, and SmithKline Beecham Laboratories, Van Nuys, California, who served as the central laboratory for the study. We thank Patience Vanderbush for editorial assistance.

ADDENDUM

At the conclusion of our primary study, a 48-week extension was undertaken for descriptive safety observations. Nine hundred seventy-seven patients from 92 of the original 362 centers participated, with patients entering if they met target levels of low-density cholesterol control. Because of the low-density cholesterol criterion, only 47 of the 977 patients remained in the placebo group. The extension study has just ended. Although not susceptible to the same level of critical analysis as the primary study, nevertheless, the results are informative. There was no material difference in the behavior of the treatment groups in the second year from that experienced in the first year either for changes in the grading of slit-lamp findings, visual acuity, or change in the number of adverse ophthalmic events. Taken together, these findings support the general conclusion made from the primary study that lovastatin gives no indication of lens toxicity in clinical usage to date.

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Effect of Left Ventricular Aneurysm on Risk of Sudden and Nonsudden Cardiac Death

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Although left ventricular (LV) aneurysm is associated with increased mortality, its independent prognostic significance is controversial. To determine the effect of LV aneurysm on risk, 121 patients with healed myocardial infarction (MI), 55 manifesting akinesia on ventriculography (MI group) and 66 with LV aneurysm characterized by diastolic deformity (eccentricity) and systolic dyskinesia (LV aneurysm group) were studied. At a mean follow-up of 5.7 years, there were 32 cardiac deaths (12 MI vs 20 LV aneurysm), including 9 sudden deaths (1 MI vs 8 LV aneurysm). Multivariate analysis revealed decreasing ejection fraction to be the best predictor of total cardiac death, and revascularization to be protective. Nonsudden cardiac death was predicted by ejection fraction, absence of revascularization and right coronary artery disease, whereas sudden cardiac death was predicted by LV aneurysm and the frequency of ventricular ectopic complexes on Holter monitoring. In the MI group, ejection fraction was the only significant predictor of total cardiac death and nonsudden cardiac death. In the LV aneurysm group, total cardiac death, as well as nonsudden cardiac death, were predicted by ejection fraction, ventricular tachycardia and right coronary artery disease, whereas ventricular tachycardia predicted sudden cardiac death. It is concluded that the risk profile for total cardiac death differs between LV aneurysm and MI patients, and that LV aneurysm constitutes an independent predictor of late sudden cardiac death after MI. Moreover, on a substrate of LV aneurysm, the risk factors for sudden cardiac death and nonsudden cardiac death differ, with ventricular tachycardia being the sole predictor of sudden cardiac death. Furthermore, Holter monitoring is valuable in identifying patients at persistent risk of sudden cardiac death.

(Am J Cardiol 1991;67:454–459)

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Although the relations between ventricular arrhythmias, left ventricular (LV) dysfunction and cardiac and sudden cardiac mortality after myocardial infarction (MI) have been studied extensively,[1–7] the prognostic significance of ventricular arrhythmias in relation to clinical, anatomic and hemodynamic characteristics on a substrate of LV aneurysm has not been addressed. Several studies have reported incidences of intractable LV failure, disabling angina and thromboembolism as high as 50%[8] and of malignant ventricular arrhythmias up to 22%[9–11] with LV aneurysm. Clinical-anatomic correlations have shown an association between ventricular tachycardia and endocardial fibroelastosis of the aneurysmal sac,[9] while septal location predicted recurrence of ventricular tachycardia.[10] Although survival data indicate higher death rates among patients with LV aneurysm than among those with uncomplicated MI, there is controversy about the independent effect of LV aneurysm on risk after adjustment for ejection fraction.[12–15] There are no data regarding differential predictive power, if any, of LV aneurysm on long-term survival and the incidence of sudden and nonsudden cardiac death. Our objective was to determine the effect of LV aneurysm on late sudden and nonsudden cardiac death after MI and to identify respective risk potentiators in the presence and absence of LV aneurysm.

METHODS

This is an historical, and in part, truly prospective study, because the cohort had been identified by 1985, with follow-up extending through January 1989. All patients with a diagnosis of LV aneurysm made during admission for evaluation of angina between 1977 and 1985 were retrospectively identified through hospital records. LV aneurysm was defined as diastolic deformity (eccentricity) and systolic dyskinesia. Sixty-six patients met these criteria for LV aneurysm: 61 (92%) by contrast and 5 (8%) by nuclear ventriculography. Each patient had a history of at least 1 MI confirmed by Q waves >30 ms on the electrocardiogram or enzymatic elevation (creatine phosphokinase MB-subunit [CPK MB] ≥15 IU/liter) or fixed defect on thallium-201 scintiscan, or all. An additional 55 patients admitted for evaluation of angina during the same period and manifesting akinesia on ventriculography were randomly selected as the control group. The mean interval between MI and time of catheterization was 1.4 years, and the minimal interval was 1 month, except for 2 patients in the LV aneurysm group, in whom aneurysm was later confirmed by nuclear ventriculography.

TABLE I Patient Characteristics

	MI Group (n = 53)	Aneurysm Group (n = 64)	p Value
Mean age (yrs)	51	51	NS
Men/women (%)	35 (65)	45 (70)	NS
Mean follow-up (yrs)	7	5	<0.05
Congestive heart failure (%)	5 (9)	18 (28)	<0.05
Unstable angina (%)	21 (40)	27 (42)	NS
Hypertension (%)	17 (32)	26 (41)	NS
Angiographic data			
Left main coronary artery >50% (%)	3 (6)	4 (6)	NS
Right coronary artery >70% (%)	31 (59)	22 (34)	<0.01
Left anterior descending artery >70% (%)	36 (68)	40 (63)	NS
Left circumflex artery >70% (%)	29 (55)	22 (34)	<0.05
Ejection fraction (mean)	50%	37%	<0.001
Ventricular ectopic complexes/hour (mean)	40	38	NS
Ventricular ectopic complexes >10/hour (%)	13 (25)	20 (31)	NS
Complex forms (%)	15 (28)	28 (44)	NS
Pairs (%)	14 (26)	18 (28)	NS
Ventricular tachycardia* (%)	7 (13)	10 (16)	NS
Medications			
Beta blocker (%)	38 (72)	41 (64)	NS
Calcium antagonist (%)	30 (57)	24 (38)	<0.05
Nitrate (%)	27 (51)	29 (46)	NS
Diuretic (%)	8 (15)	11 (17)	NS
Digitalis (%)	14 (26)	21 (33)	NS
Antiarrhythmic (%)	9 (17)	19 (30)	NS

* ≥3 sequential ventricular ectopic complexes.
MI = myocardial infarction; NS = difference not significant.

Data obtained included demographic and pertinent clinical variables (Table I). At least one 24-hour Holter monitor recording was obtained on entry or at follow-up for 113 patients (93%), and an 8- or 12-hour Holter monitor or telemetry strips were obtained for the remaining 8 (7%). Holter recordings obtained within 2 weeks of an MI were excluded. When more than 1 study was available, we used the 1 with the higher degree of ectopy. By means of cineventriculograms in the 30° right and left anterior oblique positions or gated blood pool scintigrams in the anterior, left anterior oblique and lateral positions, or both, the left ventricle was divided into anterior-lateral, posterior-inferior and apical-septal segments, which were characterized as normokinetic, hypokinetic, akinetic or dyskinetic. The extent of coronary disease was coded by the vessel(s) involved and the degree of stenosis.

The follow-up interval was defined as beginning on the date of the first MI and ending in January 1989, unless concluded earlier because of loss of contact or death. Information on follow-up events and outcome was obtained through outpatient visits, inpatient records and telecommunication with patients, family members or primary physicians. Noncardiac deaths were excluded (2 per group). Fatal outcome was classified as sudden cardiac death or nonsudden cardiac death. We defined as sudden, deaths that occurred within 1 hour of symptom onset. When acute MI or LV failure was the cause, death was not considered sudden, even if it occurred within 1 hour.

Statistical analysis: The groups were compared using Student's *t* test for continuous measures and chi-square for categorical variables. Survival analysis (Statistical Package for the Social Sciences—X), logistic regression and the Cox proportional-hazards model (Statistical Analysis Systems) were used to identify predictors of total cardiac death (nonsudden plus sudden cardiac death), nonsudden and sudden cardiac death among the total population and within each group (MI and LV aneurysm). On the premise that risk factors and their respective operative mechanisms leading to sudden and nonsudden cardiac death may differ or be mutually exclusive or interfering, nonsudden cardiac deaths were censored from the analysis of sudden cardiac death and vice versa.[2] The null hypothesis was rejected for $p < 0.05$, although in some instances $p < 0.10$ was considered to be statistically significant owing to the relatively small sample size and the clinical relevance or importance of the predictor variable.

RESULTS

Clinical characteristics for both groups are compared in Table I. Age ranged from 21 to 80 years. There were no group differences in the prevalence of diabetes mellitus, and alcohol or tobacco use. Apical-septal was the predominant aneurysm location (apical-septal 91%, anterior-lateral 39%, posterior-inferior 24%).

Follow-up and outcome: Mean follow-up was similar for both groups. Of 21 patients (12 MI vs 9 LV aneurysm) who had subsequent MI, 12 died (4 MI vs 8 LV aneurysm). Of 25 patients (14 MI vs 11 LV aneurysm) who underwent revascularization (4 before and 21 after the initial MI), 3 died (0 MI vs 3 LV aneurysm). Of 9 patients (14%) who had aneurysmectomy, 4 died (44%), 1 suddenly (11%). Although the number of aneurysmectomy cases was too small to allow for meaningful comparison, this procedure tended not to protect against sudden or nonsudden cardiac death. Compared to the total population, the sudden cardiac death rate

TABLE II Incidence of Sudden, Nonsudden and Total Cardiac Death in Myocardial Infarction and Aneurysm Groups Compared to Total Population

	Total Population (n = 117)	MI Group (n = 53)	Aneurysm Group (n = 64)
Total cardiac death	32/117 (27%)	12/53 (23%) NS	20/64 (31%) NS
Nonsudden cardiac death	23/108 (21%)	11/52 (21%) NS	12/56 (21%) NS
Sudden cardiac death	9/94 (10%)	1/42 (2%) p <0.01	8/52 (15%) p <0.05

Abbreviations as in Table I.

was significantly lower in the MI group and significantly higher in the LV aneurysm group (Table II). With either total or sudden cardiac death taken as end points, cumulative survival did not differ between the groups in the first 4 years (Figures 1 and 2). Survival curves diverged thereafter, with cardiac and sudden cardiac mortality being higher with LV aneurysm.

Univariate analysis: In the MI group, there were no differences in clinical characteristics between total cardiac death and survivors. However, the ejection fraction tended to be higher among survivors ($p = 0.08$). In this group, the only patient who died suddenly had 242 ventricular ectopic complexes per hour and an ejection fraction of 59%, compared to a mean of 43 ventricular ectopic complexes per hour and mean ejection fraction of 58% among survivors. In the LV aneurysm group, there were differences between survivors and nonsudden cardiac death in ejection fraction ($p < 0.05$), incidence of ventricular tachycardia (≥ 3 sequential ectopic complexes, $p < 0.05$), and between survivors and sudden cardiac death, there were differences in ventricular ectopic complexes per hour ($p < 0.05$), incidence of ventricular tachycardia ($p < 0.05$) and frequency of use of digitalis ($p < 0.05$).

Multivariate analysis: Multivariate logistic regression identified predictors of total cardiac, nonsudden and sudden cardiac death for the total population, the MI group and the LV aneurysm group (Table III). Decreasing ejection fraction predicted nonsudden and total cardiac death for all patients and the subgroups. It was, specifically, the most significant predictor of total cardiac death for all patients. However, it failed to predict sudden cardiac death for all patients or the subgroups. In contrast, LV aneurysm was the most significant predictor of sudden cardiac death for all patients. Although ventricular tachycardia, by itself, predicted sudden cardiac death for the total population ($p = 0.048$), it was no longer significant after adjustment for LV aneurysm. In the LV aneurysm group, however, ventricular tachycardia was the sole predictor of sudden cardiac death.

Revascularization conveyed a protective effect in relation to total cardiac and nonsudden cardiac death for the total population, but had no impact on sudden cardiac death. We further explored the protective effect of revascularization for nonsudden cardiac death by making a distinction between surgery before and surgery after the first MI. Coronary artery bypass grafting continued to be protective in a multiple logistic model, but could not be statistically confirmed to be related to the length of survival in a Cox proportional-hazards model.

DISCUSSION

Although radionuclide and cineventriculography have enabled antemortem recognition of LV aneurysm, no standard criteria exist for diagnosis. Anatomic aneurysm manifests itself as diastolic convex protrusion.[16] In systole, it may exhibit paradoxical motion (dyskinesia) or its diameter may not change (akinesia). Earlier, dys-

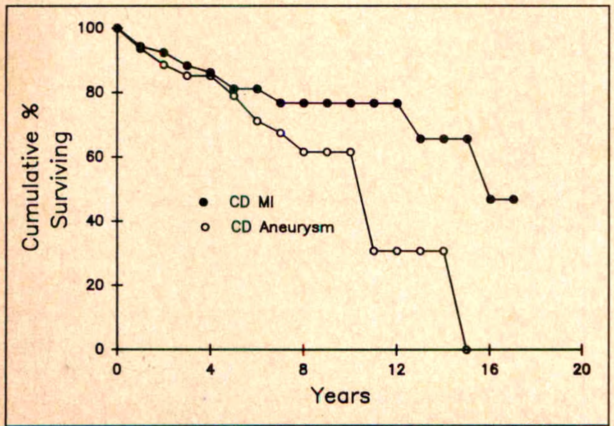

FIGURE 1. Cumulative percent survival comparing aneurysm and myocardial infarction (MI) groups for total cardiac death (CD).

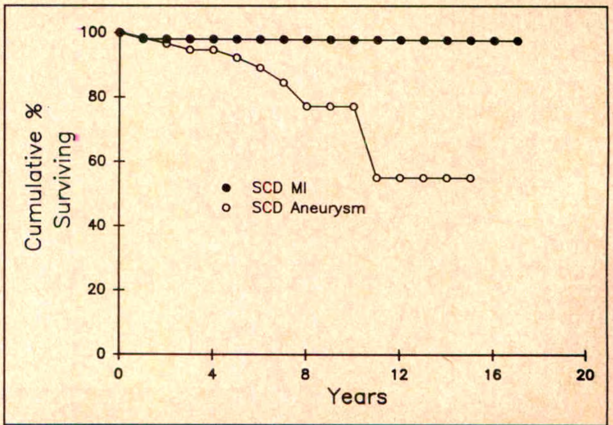

FIGURE 2. Cumulative percent survival comparing aneurysm and myocardial infarction (MI) groups for sudden cardiac death (SCD).

TABLE III Predictors of Cardiac Death

	Predictor	Odds Ratio	p Value
	Total Population* (n = 117)		
Total cardiac death (n = 32/117)	Decreasing ejection fraction†	1.05	0.004
	Revascularization	0.12	0.042
Sudden cardiac death (n = 9/94)	LV aneurysm	10.1	0.048
	Ventricular ectopic complexes/hour†‡	2.27	0.06
Nonsudden cardiac death (n = 23/108)	Decreasing ejection fraction	1.05	0.01
	Revascularization	N.E.§	0.001‖
	Right coronary artery stenosis >70%	2.64	0.064
	Aneurysm Group (n = 64)		
Total cardiac death (n = 20/64)	Ventricular tachycardia	8.43	0.01
	Decreasing ejection fraction	1.06	0.03
	Right coronary artery stenosis >70%	2.93	0.10
Sudden cardiac death (n = 8/52)	Ventricular tachycardia	11.9	0.02
Nonsudden cardiac death (n = 12/56)	Ventricular tachycardia	12.8	0.02
	Decreasing ejection fraction	1.08	0.04
	Right coronary artery stenosis >70%	7.83	0.02
	MI Group (n = 53)		
Total cardiac death (n = 12/53)	Decreasing ejection fraction	1.05	0.08
Nonsudden cardiac death (n = 11/52)	Decreasing ejection fraction	1.06	0.05

* Excluding 2 noncardiac deaths in each group.
† The risk of mortality increases with each percent point decrease in ejection fraction. An odds ratio of 1.05 indicates a 5% increase in risk for each 1% decrease in ejection fraction, whereas an odds ratio of 1.08 indicates an 8% increase in risk per 1% decrease in ejection fraction.
‡ In cases where the number of complexes was 0, the natural log of the number was set to equal 0.
§ No revascularized patient had nonsudden death, thereby making the odds ratio nonestimable (N.E.).
‖ Determined by comparing the log likelihood ratios of models with and without the revascularization predictor.
Predictors approaching the 0.05 significance level were included when odds ratios were large or clinically significant.
LV = left ventricular; MI = myocardial infarction.

kinesia without diastolic deformity (functional aneurysm) was considered sufficient for diagnosis.[13,17] More recently, diastolic deformity was added as a prerequisite for LV aneurysm.[12,14] In the absence of anatomic aneurysm, differentiation between dyskinesia and akinesia can be made by graphic analysis, although several factors, including the contractile status of the adjacent myocardium[17] and possible change in heart position between diastole and systole, may mask the presence of or simulate dyskinesia. For this reason, our study excluded patients manifesting functional aneurysm alone. Furthermore, we did not encounter any cases of anatomic aneurysm without dyskinesia. Meizlish et al[15] added "normal adjacent myocardium" as a third criterion, with probable increase in specificity. However, Alexopoulos et al[12] observed that the addition of "normal adjacent myocardium" decreased the sensitivity in identifying aneurysm in patients with a recent anterior MI.

Although increased cardiac mortality is recognized, it is unclear whether LV aneurysm constitutes an independent risk, or whether death rate is solely a function of ejection fraction and other variables conveying risk after MI. Using an impressively large cohort from the Coronary Artery Surgery Study registry, Faxon et al[14] showed that the 5-year mortality from LV aneurysm exceeded that of the control group, but the difference was negligible with adjustment for ejection fraction. Unfortunately, their control group was quite heterogeneous; only 50% had a prior infarction, and the criterion for entry was defined as ≥50% narrowing of the luminal diameter of any major coronary arterial segment. At follow-up of 2 groups manifesting akinesia or dyskinesia, Cohen and Vogel[13] also found no difference in death rate at 3 years from the date of cardiac catheterization. However, Meizlish et al[15] observed that the early, as well as 1-year, post-MI mortality was significantly higher in patients with aneurysm than in those without. The contrast between these studies[13–15] is striking and may be explained, at least in part, by differences in design. Given the prevalence of low ejection fraction in aneurysm, and the colinearity between low ejection fraction and aneurysm, use of a control group with a high mean ejection fraction could add substantial bias. In the population of Faxon et al, 74% of the control, compared to 32% of the aneurysm group, had an ejection fraction >50%, whereas in the Meizlish cohort the mean ejection fraction was 30% and did not differ between the aneurysm and MI groups. In the Faxon and Cohen reports, the MI was remote, and survival was referenced to the time of cardiac catheterization, whereas the study of Meizlish et al[15] was truly prospective, with follow-up starting not later than 48 hours after the initial anterior MI. In the latter study, although aneurysm was diagnosed in only 35% of 51 patients, despite

extensive necrosis as suggested by the total population's mean creatine phosphokinase MB-subunit of 250 IU/liter and very low ejection fraction, the 1-year mortality among these patients was 61%. Thus, aside from losses and gains in regard to sensitivity and specificity for aneurysm, Meizlish et al[15] were successful in identifying a high-risk population. Our cohort was identified from cardiac catheterization records and excluded patients not surviving long enough to undergo catheterization or those who were asymptomatic after the initial event. Survival length was measured from the time of the initial MI. In accordance with Faxon et al,[14] we showed decreasing ejection fraction to be an independent predictor of total cardiac death and nonsudden cardiac death in the total population and in stratified analysis for both the LV aneurysm and the MI groups (Table III). In contrast, ejection fraction did not predict sudden cardiac death in the total population or in the LV aneurysm group, which suggests that in the presence of LV aneurysm the predictive features of sudden cardiac death and nonsudden cardiac death differ (Table III).

The incidence rate of cardiac death and nonsudden cardiac death did not differ between the total population and the MI and LV aneurysm subgroups. In contrast, the incidence of sudden cardiac death was low with uncomplicated MI and high with LV aneurysm (Table II). The low rate of *late* sudden cardiac death in the MI group agrees with that of previous reports by Mukharji et al,[5] whose MILIS Study Group found the overall incidence of sudden cardiac death to be 1.4% after 6 months, whereas Moss et al[18] observed that sudden cardiac death predominates in the first 6 to 8 months after MI. However, our finding that *late* sudden cardiac death represented 40% of cardiac deaths in the LV aneurysm group, and that its incidence was eightfold higher than in the MI group, is striking and previously unreported. Meizlish et al[15] noted a tendency toward a higher rate of early sudden cardiac death in LV aneurysm, whereas the study of Faxon et al[14] showed no difference. However, ≥50% of the control group in the Faxon study had significant coronary artery disease without previous MI and thus a potentially ischemic and electrically unstable myocardium.

Several studies showed ventricular ectopy to be an independent predictor of total cardiac death[4,19,20] and sudden cardiac death[2,5] after MI. Others suggested that the effect of ventricular arrhythmias on risk is overwhelmed by indexes of LV function and functional impairment due to congestive heart failure.[3] In our study, of the 17 patients who exhibited ventricular tachycardia in both groups, 47% had cardiac death, 29% nonsudden cardiac death and 18% sudden cardiac death. Of the 10 patients with ventricular tachycardia in the LV aneurysm group, 70% had cardiac death, 40% nonsudden cardiac death and 30% sudden cardiac death. Multivariate analysis showed that ventricular tachycardia was powerful in predicting total cardiac death, nonsudden cardiac death and sudden cardiac death in LV aneurysm, and that it was specifically the *sole* predictor of sudden cardiac death in this group (Table III). The ability of ventricular tachycardia to predict all forms of cardiac death in the LV aneurysm group supports the thesis that an association exists between ventricular tachycardia and LV dysfunction.[3] In addition, the inability of ejection fraction to predict sudden cardiac death and the power of ventricular tachycardia to be the sole predictor of sudden cardiac death in LV aneurysm strongly suggests specific relations among ventricular arrhythmias, LV aneurysm and sudden cardiac death. The finding that ventricular tachycardia was not an independent risk factor of sudden cardiac death in the total population is at least partly due to the fact that 89% of sudden cardiac death occurred in patients with LV aneurysm, which overwhelmed other risks for sudden cardiac death. Furthermore, the finding that the number of ventricular ectopic complexes per hour was a predictor, albeit weak, of sudden cardiac death for the total population is in accordance with the findings of Bigger and Weld[21] and suggests that the frequency of ventricular extrasystoles contributes significant additional risk for death even in the 3 highest Lown grades. Use of digitalis was much more frequent among sudden cardiac deaths than among survivors in the LV aneurysm group (63 vs 23%, $p < 0.05$), whereas the prevalence of congestive heart failure and the mean ejection fraction did not differ. Thus, although digitalis did not independently predict sudden cardiac death, its possible contribution to fatal arrhythmias cannot be excluded.

Limitations of 24-hour Holter monitoring due to therapeutic intervention and biologic or spontaneous variation were inevitable,[22] even though in several patients more than 1 study was available. This may explain the very low sensitivity of ventricular tachycardia in identifying patients who subsequently sustained cardiac death (8.3%), nonsudden cardiac death (9%) and sudden cardiac death (0%) in the MI group. However, although the incidence of ventricular tachycardia was similar in the 2 groups (Table I), a fourfold or higher sensitivity of ventricular tachycardia in identifying patients who subsequently had cardiac death (35%), nonsudden cardiac death (33%) and sudden cardiac death (38%) was observed in the LV aneurysm group, which suggests that the influence of these variations is less important in the presence of LV aneurysm. Furthermore, the specificity of ventricular tachycardia in identifying patients at risk for late death in the LV aneurysm group was extremely high (93%).

Finally, our finding that right coronary artery disease is a predictor of nonsudden cardiac death in the LV aneurysm group may reflect more myocardium in jeopardy, because the majority of patients also had left anterior descending artery disease. This is consistent with the report by Schulman et al,[23] who found that right coronary artery plus left anterior descending artery stenoses >70% predicted poor outcome.

Censoring of nonsudden cardiac deaths from the analysis of sudden cardiac death and vice versa enabled the detection of differences in risk factor profiles between these types of death in patients with LV aneurysm and uncomplicated MI. Although ventricular arrhythmias are a nonspecific manifestation of LV dysfunction after uncomplicated MI, specific relations do

exist among LV aneurysm, malignant arrhythmias and sudden cardiac death.

In summary, the risk of *late* sudden cardiac death is small after uncomplicated MI, but significant in the presence of LV aneurysm. With or without LV aneurysm, the ejection fraction predicts late nonsudden cardiac death, but fails to predict sudden cardiac death. In the presence of LV aneurysm, ventricular tachycardia is the *sole* predictor of late sudden cardiac death. Given the high specificity of ventricular tachycardia in identifying subsequent cardiac deaths in patients with LV aneurysm and the persistent risk of sudden cardiac death, 24-hour Holter monitoring is valuable for risk stratification, treatment and long-term follow-up in this subgroup of post-MI patients.

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Angiographic Morphology in Unstable Angina and Its Relation to Transient Myocardial Ischemia and Hospital Outcome

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Complex stenosis morphology frequently occurs in patients with unstable angina pectoris. However, its relation to transient myocardial ischemia and hospital outcome has not been ascertained. To address this issue, 88 patients with significant (≥50%) coronary artery disease presenting with angina—new onset (n = 38), worsening (n = 20) or at rest (n = 30)—were studied. Patients with left main artery disease, normal coronary arteries or occlusion of the ischemia-related arteries were not included in the study. Continuous electrocardiographic recordings were obtained during the first 24 hours. Angiography was performed within 1 week from admission. Complex morphology was defined as any stenosis with irregular borders, overhanging edges or intracoronary thrombus. Only data referring to the in-hospital outcome were considered in this study. Adverse end points were sudden death, myocardial infarction and emergency revascularization. Analysis of the angiograms revealed a complex morphology in 58 patients (group 1). The remaining 30 patients served as control subjects (group 2). Thirty-two of the 58 group 1 patients had an unfavorable clinical outcome (positive predictive value, 55%). A similar outcome occurred in only 2 of the 30 group 2 patients (negative predictive value, 93%). Of the 32 group 1 patients who had an unfavorable clinical outcome, 29 had a cumulative duration of transient myocardial ischemia of ≥60 minutes per 24 hours. A similar duration of ischemia, however, was observed in another 6 group 1 and in 8 group 2 patients. Thus, association of complex coronary morphology with sustained (≥60 minutes per 24 hours) myocardial ischemia is highly predictive of subsequent coronary events (positive and negative predictive value, 83 and 91%, respectively), compared with the absence of 1 or both findings.

(Am J Cardiol 1991;67:460–464)

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Unstable angina is an inhomogeneous syndrome. A substantial percentage of patients, ranging from 12 to 30% in most series, develops acute myocardial infarction or dies suddenly soon after their hospitalization, while the remainder have a benign prognosis without adverse coronary events.[1] Considerable efforts are therefore under way to separate patients into a manageable number of meaningful subgroups based on the severity of the disease, which would facilitate the choice of appropriate diagnostic measures and therapeutic options for individual patients.[2] Recent evidence indicates that angiography reveals in many patients with an unfavorable clinical outcome an eccentric and irregular coronary stenosis[3] often associated with filling defects because of intraluminal thrombi.[4] However, the prognostic significance of these findings is still uncertain; hence, the decision process concerning the use of emergency coronary angiography and revascularization in the overall population of patients presenting with unstable angina remains controversial.[5,6] The purpose of the present study was twofold: first, to assess prospectively the immediate in-hospital morbidity and mortality in patients with unstable angina as well as documented coronary morphology; second, to identify the historical, clinical and electrocardiographic correlates of each possible angiographic finding that could indicate a high risk of impending myocardial infarction and death and hence the need for ongoing emergency coronary angiography and revascularization.

METHODS

We prospectively studied 116 patients admitted to our coronary care unit from November 1986 to July 1989 with unstable angina, defined as: (1) new onset (within 1 month); (2) worsening (progressive effort angina sufficiently severe to warrant hospital admission); (3) at rest (including prolonged chest pain). Criteria for exclusion from the study were: age >75 years, uninterpretable electrocardiogram, adverse outcome owing to concomitant nonmyocardial diseases, severe heart failure, and absence of ST-T changes during chest pain. Patients who developed an acute myocardial infarction in the first 24 hours were not enrolled in the study. All patients were initially treated with a standard medical regimen: intravenous nitroglycerin (10 to 40 μg/min), oral calcium antagonists (verapamil 240 to 360 mg/day), β blockers (propranolol 60 to 240 mg/day), and oral aspirin (325 mg/day). Also, 0.5 mg of intravenous nitroglycerin or 5 mg of sublingual isosorbide dinitrate

were used as required. None of the patients had bradycardia or ventricular dysfunction during medical therapy.

Holter and creatine kinase monitoring: Continuous 2-channel electrocardiographic monitoring was performed in the coronary care unit during the first 24 hours of medical therapy (Applied Cardiac System 8300 frequency-modulated recorders; frequency response 0.05 to 100 Hz). The 2 leads showing the most pronounced reversible ischemic changes on the initial qualifying 12-lead electrocardiogram were selected for analysis. Recordings were printed in a minielectrocardiogram format by a Telemed Saturn 3200 analyzer. Holters were read by investigators blinded to the clinical data. Only episodes lasting >60 seconds and with ≥0.15 mV of ST-segment shift were considered for analytic purposes. The number and duration of symptomatic ischemic episodes were recorded in angina diaries. All recordings were performed while patients were resting in bed. Serial plasma creatine kinase and its MB isoenzyme estimations were performed every 4 hours for ≥24 hours. Acute myocardial infarction was diagnosed if the serial enzyme measurements showed an elevation of creatine kinase >2 times normal with MB fraction >6%.

Coronary angiography: Within 1 week from admission (range 4 to 7 days), all patients underwent left-sided cardiac catheterization, which was performed with standard catheters and techniques. Each coronary artery was selectively viewed in ≥2 projections. Quantitative and qualitative analyses of the end-diastolic cine frames were performed by 2 teams, each comprising 2 observers experienced in angiographic interpretation and blinded to the clinical data. Differences were mediated by consensus. A stenosis ≥50% was considered significant. Complex angiographic morphology was defined as any significant asymmetric stenosis with irregular borders or overhanging edges or intraluminal thrombus (Figure 1). Correlation between electrocardiographic changes during angina and coronary anatomy at angiography has been described elsewhere.[3] When recognition of the ischemia-related stenosis was uncertain, the most severe narrowing of the artery was chosen for analysis. Patients with coronary occlusion of the ischemia-related artery or with normal coronary arteries, in whom morphology could not be assessed, were excluded from angiographic evaluation. Patients presenting with significant left main coronary artery disease were also excluded from the study, because their prognosis is well established and does not require further investigation.

Follow-up and prognostic end points: Only data referring to the in-hospital outcome were considered for this study. Cardiac events were defined as cardiac death, myocardial infarction or emergency revascularization, i.e., either coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. The decision to perform emergency revascularization in the absence of significant left main coronary artery disease was made according to protocol on the basis of the patient's symptomatic behavior. Emergency revascularization required (1) recurrent (>3 times per day) chest pain with accompanying electrocardiographic changes of ischemia despite complete bedrest and medical regimen for ≥2 days after the first 24 hours in the hospital, and (2) suitable as well as severe (stenosis >70%) coronary artery disease.

Statistical analysis: We analyzed both quantitative and qualitative features. The former were expressed as mean ± standard deviation and comparisons were made by Student's *t* test for unpaired data. The latter were expressed as percentages and for statistical inference were arranged in 2 × 2 contingency tables, and chi-square with Yates correction method was used. The Fisher exact test was also applied when appropriate. A p value <0.05 was considered statistically significant.

RESULTS

Coronary arteriographic findings: Coronary angiography was suitable for qualitative analysis of the stenosis in 88 of the 116 patients. Twenty-eight patients were excluded: 7 had normal coronary arteries, 4 had a total occlusion of the ischemia-related artery, 5 presented significant left main artery disease, and the ischemia-related artery was not detectable in 12. Coronary lesions were morphologically classified using the criteria of Ambrose et al.[3] Coronary stenosis was concentric in 9 patients (10%), eccentric with smooth borders and a broad neck (type 1) in 17 (19%), and eccentric with irregular borders or overhanging edges (type 2) in 58 (66%); 4 patients (5%) had multiple irregularities. Evidence of coronary thrombus by angiographic criteria[7] was found in 19 patients (22%); all had a type 2 stenosis. The 58 patients with type 2 stenosis or thrombus, or both, were considered to have "complex morphology" (group 1). The remaining 30 patients served as control subjects (group 2). Extension of coronary artery disease was expressed by the number of arteries with stenosis >50%. No differences were found between the 2 groups (Table I), with the exception of the mean coronary nar-

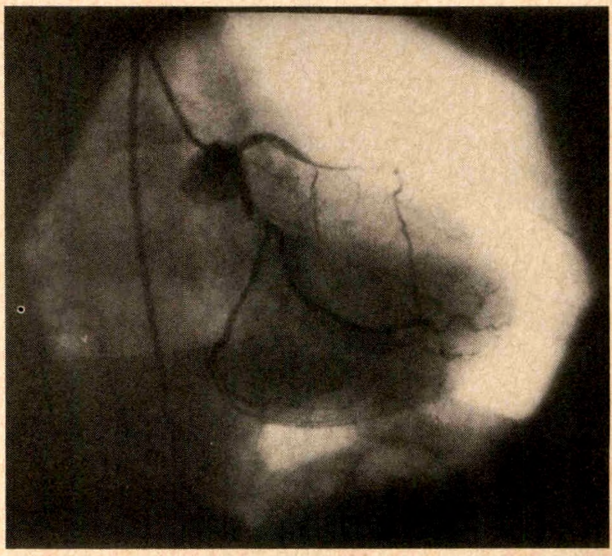

FIGURE 1. Complex coronary stenosis in a patient with unstable angina. A large thrombus adherent to an eccentric stenosis with irregular borders can be seen in the circumflex branch of the left coronary artery.

TABLE I Patients with Unstable Angina Pectoris With and Without Complex Coronary Morphology

	Complex Morphology (+) (n = 58)	Complex Morphology (0) (n = 30)	p Value
Angiographic Data			
Mean % IRA stenosis	89 ± 10	75 ± 20	<0.00001
CA with narrowing >50%	1.98 ± 0.85	1.83 ± 0.70	
One-vessel CAD (%)	21 (36)	10 (33)	
Two-vessel CAD (%)	17 (29)	15 (50)	
Three-vessel CAD (%)	20 (35)	5 (17)	
Ejection fraction (mean %)	64 ± 10	66 ± 11	
Clinical Data at Admission			
Age (yr)	60 ± 7	57 ± 7	
Gender (male %)	49 (84)	27 (90)	
Previous history of CAD (%)	28 (48)	18 (60)	
Pattern of pain at presentation (%)			
Recent onset angina	8 (14)	10 (33)	
Worsening angina	8 (14)	12 (40)	<0.05
Rest angina	24 (41)	6 (20)	
Postinfarction angina	18 (31)	2 (7)	<0.02
In-hospital therapy			
IV nitroglycerin (μg/min)	35 ± 12	29 ± 15	
Propranolol (mg/day)	158 ± 43	163 ± 55	
Verapamil (mg/day)	275 ± 61	263 ± 59	
Aspirin (mg/day)	325	325	
In-Hospital Electrocardiographic Data			
Pain during ECG monitoring (%)	47 (81)	13 (44)	<0.05
ST shift (%)			
ST elevation	24 (41)	12 (40)	
ST depression	25 (43)	16 (53)	
Both	9 (15)	2 (7)	
Duration of TMI at admission (min/24 hrs)	84 ± 59	37 ± 27	<0.001
In-Hospital Adverse Cardiac Events			
Total events (%)	32 (55)	2 (7)	<0.00001
Major coronary events (%)	10 (17)	0 (0)	<0.001
Nonfatal AMI	6 (10)	0 (0)	
Cardiac death	4 (7)	0 (0)	
Emergency revascularization (%)	22 (38)	2 (7)	<0.001
CABG	15 (26)	2 (7)	<0.05
PTCA	7 (12)	0 (0)	<0.05

AMI = acute myocardial infarction; CA = coronary arteries; CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiographic; IRA = ischemia-related artery; IV = intravenous; PTCA = percutaneous transluminal coronary angioplasty; TMI = transient myocardial ischemia.

rowing of the ischemia-related artery, which was seen to be greater in group 1 than in group 2.

Relation between angiographic morphology and clinical features: The clinical characteristics of the 88 patients comprising the study population are listed in Table I. Eighteen patients (31%) in group 1 had a history of postinfarction angina; only 2 group 2 patients had such a history (Table I). The pattern of pain at presentation also differed between the 2 groups. Most patients in group 1 had pain at rest, but significantly fewer patients in group 1 had a history of progressive effort pain. Holter monitoring analysis (Table I) revealed reversible ST-T-segment changes documented at admission in 100% of group 1 and 90% of group 2 patients. More group 1 than group 2 patients presented with pain during electrocardiographic monitoring. Also, the cumulative duration of ischemia over 24 hours was consistently greater in group 1 than in group 2 patients (84 ± 59 vs 37 ± 27 min, $p < 0.001$). Thirty-five patients in group 1 (60%) and 8 patients in group 2 (27%) had a cumulative transient ischemia duration of ≥60 minutes per 24 hours after admission ($p < 0.01$). Clinical outcomes are summarized in Table I. Before hospital discharge, 6 patients had a nonfatal myocardial infarction (all in group 1) and 4 died (all in group 1), 1 from myocardial infarction and 3 suddenly. Emergency coronary revascularization was performed in 24 patients (22 group 1 and 2 group 2 patients). Overall, adverse coronary events occurred in 55% of group 1 versus 7% of group 2 patients.

Clinical and angiographic predictors of adverse clinical outcome: Thirty-two of the 58 group 1 patients had an unfavorable clinical outcome (positive predictive

TABLE II Clinical and Angiographic Predictors of In-Hospital Adverse Cardiac Events			
	Complex Morphology	TMI (≥60 min/24 hrs) + Complex Morphology	p Value
Sensitivity (%)	94	85	
Specificity (%)	52	89	<0.001
Positive predictive value (%)	55	83	<0.02
Negative predictive value (%)	93	91	
Accuracy (%)	68	88	<0.005

TMI = transient myocardial ischemia.

value, 55%). Subsequent adverse coronary events occurred in only 2 of the 30 group 2 patients (negative predictive value, 94%). Twenty-nine of the 32 group 1 patients (91%) who had an unfavorable clinical outcome had a cumulative duration of ischemia ≥60 minutes per 24 hours (Figure 2). A similar duration of ischemia, however, was also observed in 13 other patients who later had a good prognosis (6 group 1 and 7 group 2 patients) and in 1 more patient (group 2) who had subsequent coronary events. Thus, association of sustained myocardial ischemia (≥60 minutes per 24 hours) with complex morphology was a better predictor of subsequent coronary events (positive and negative predictive value, 83% and 91%, respectively), compared to the absence of 1 or both findings (Table II).

DISCUSSION

Our data are of practical importance in the management of unstable angina. First, they provide further confirmation[3,6] that coronary stenosis with complex morphology are frequently found in patients (66%) referred to the coronary care unit because of chest pain. Second, they indicate that such coronary lesions are really "ischemia producing," as they are often associated with a greater extent (≥60 minutes per 24 hours) of ST-segment shifts. Third, there is a strict relation between the occurrence of such angiographic and electrocardiographic features, and early clinical outcome. Association of sustained myocardial ischemia, despite medical therapy, with complex stenosis morphology is highly predictive of subsequent coronary events, compared to the absence of 1 or both findings.

Prognostic significance of coronary morphology: Our results are comparable to those reported in recent studies,[6] and demonstrate that the need for urgent revascularization prompted by recurrent symptoms, or the occurrence of in-hospital cardiac events (sudden death or myocardial infarction), is often (94%) associated with a complex morphology stenosis of the ischemia-related artery, if such patients have either high-grade multivessel disease or minimal coronary artery disease. The same angiographic finding, however, can be found in a substantial portion (45%) of patients with a good clinical outcome. This may cause uncertainty as to how to establish risk adequately, and arouses concern as to whether all patients with documented complex coronary morphology should undergo emergency coronary bypass surgery or angioplasty. These procedures have been shown to have a higher rate of major complications, compared to that detectable during elective coronary revascularization.[8,9]

Relation between angiographic morphology and extent of myocardial ischemia: The fact that patients with persistent angina refractory to medical treatment form a high-risk group is well established.[10] Other studies indicate that the elimination of symptoms alone may not ensure a favorable outcome[11,12] and demonstrate that an arbitrary classification of silent ischemia ≥60 minutes per 24 hours in duration, as detectable in the first 24 to 48 hours of intensive medical therapy, is associated with an unfavorable early prognosis.[13] The significance of ST-segment shift with respect to coronary anatomy and in-hospital outcome was also evaluated in a recent study, which showed that the duration of ischemia was greater in patients with an unfavorable outcome, multivessel disease and left main artery steno-

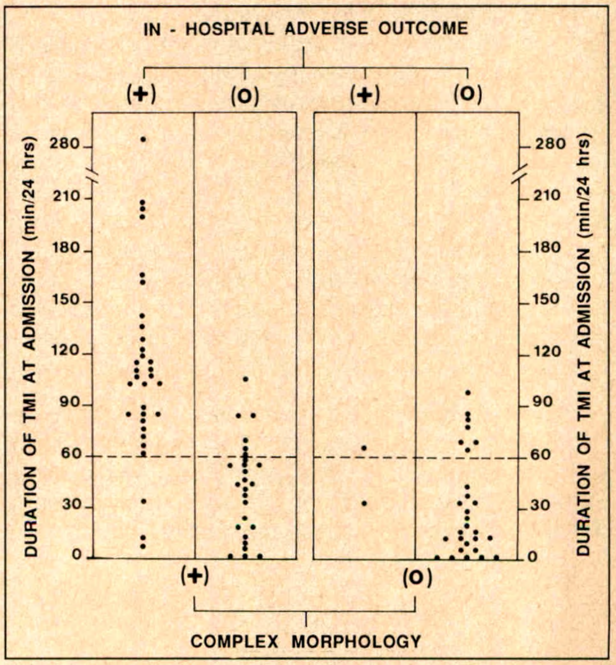

FIGURE 2. Relations among complex stenosis morphology, transient myocardial ischemia (TMI), and in-hospital outcome in patients with unstable angina. Concurrency of complex stenosis morphology with TMI ≥60 minutes per 24 hours is highly predictive of subsequent adverse coronary events.

sis.[14] In the present study, however, the use of electrocardiographic monitoring does not completely fulfill the criteria to prospectively establish a modeling strategy for emergency revascularization. This requires a high methodologic sensitivity and specificity. The latter, conversely, is relatively low, because a cumulative duration of ischemia ≥60 minutes in the first 24 hours from admission was detectable in numerous patients (13 of 54) who later had a good prognosis. Data from Holter monitoring can, however, stratify patients if combined with those obtained by coronary angiography. Accordingly, the results of statistical analysis indicate that the association of persistent (≥60 minutes per 24 hours) myocardial ischemia, despite medical treatment, with complex stenosis morphology was highly predictive of subsequent coronary events; thus, this association is potentially suitable as a guideline for emergency revascularization. This is well illustrated by the following data: The positive and negative predictive values of this association between findings were 83 and 91%, respectively. Sensitivity was 85 and specificity 89%. Also, the incidence of false positive results was extremely low (6 patients, 7%) if compared to that calculated in the absence of 1 of such findings (17 and 26 patients, 19 and 30%). Also, the cost of missed patients (i.e., false-negative results) does not seem to be relevant (5 patients, 6%).

Pathogenetic and clinical implications: It is conceivable that the impact of these 2 features (i.e., complex stenosis morphology and persistent myocardial ischemia) on prognosis may be additive, because one could define an initiating mechanism (i.e., plaque disruption),[15] and the other the result of its interaction with concurrent precipitating factors underlying rapid plaque progression toward coronary occlusion. This is in keeping with the observation that the ultimate fate of plaque rupture seems to depend on many variables, such as the degree of the preexisting chronic obstruction, the development of a local coronary vasoreactivity,[16] and the extent of intracoronary thrombosis.[17] Thrombus formation has been found to be a dynamic process in which it waxes and wanes in size over hours and days,[18] which may itself explain different degrees of coronary subocclusion and related ischemia. Accordingly, a combination of qualitative anatomic findings and electrocardiographic data on ischemia seems to provide a potent method to assess risks in patients with unstable angina.

Acknowledgment: We are indebted to Giuseppe Cavicchi for statistical assistance, to Carla Gamberini for technical assistance, to Alessandra Gozzi, Monica Salomoni and Paolo Baldazzi for nursing assistance, and to Vincenza Saccone for manuscript preparation.

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Anginal Symptoms Without Ischemic Electrocardiographic Changes During Ambulatory Monitoring in Men With Coronary Artery Disease

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Episodes of angina pectoris without electrocardiographic (ECG) signs of myocardial ischemia during 24-hour ambulatory monitoring were studied in 128 patients with a history of stable angina, angiographically proven coronary artery disease and positive exercise test results. In all, 341 episodes of ischemic ECG changes (ST-segment depression >1 mm for >1 minute) and 190 episodes of angina pectoris were observed: 86 episodes consisted of both ECG changes and angina pectoris, 255 episodes consisted only of ECG changes, and 104 episodes only of angina pectoris. Duration and magnitude of ST-segment deviation and heart rate at the onset of ischemia were similar in the 86 symptomatic and the 255 asymptomatic episodes with ECG changes.

The 104 episodes of angina pectoris without ECG changes were detected in 44 patients (34%) (group A); 29 of them had only episodes with angina pectoris and 15 patients had both—episodes of angina pectoris with and without ECG changes. In 84 patients (66%) (group B) angina pectoris without ECG changes was not observed; all episodes were accompanied by ischemic ECG changes in these patients. No differences in the angiographic extent of coronary artery disease and in exercise test data were seen in both groups A and B; however, maximal ST-segment depression during exercise testing was significantly greater in group B than in group A patients (2.4 ± 0.8 mm vs 1.9 ± 0.9 mm; p <0.05).

It is concluded that in patients with stable angina pectoris and positive exercise test results, anginal episodes can occur in the absence of ischemic ECG changes during ambulatory monitoring; in patients having episodes with ECG changes during ambulatory monitoring, angina without ECG changes most probably is ischemic in origin and should be included when estimating the extent of myocardial ischemia.

(Am J Cardiol 1991;67:465–469)

Ambulatory monitoring of the electrocardiogram is widely used in evaluating spontaneous ischemic episodes during the patient's daily activities.[1–3] Assessment of "total ischemic burden"[4] by this technique has been applied to predict prognosis[5–7] and to study the effect of antiischemic drug treatment.[8,9]

However, compared with other techniques used to diagnose ischemia such as thallium stress scintigraphy,[10,11] radionuclide ventriculography[12] or positron emission tomography,[13] the electrocardiogram proved to have a relatively low sensitivity. This is especially true for stress electrocardiography in which ST-segment depression is known as an equivalent occurring late in the evolution of ischemia.[14] Episodes of myocardial ischemia may also be missed during ambulatory electrocardiographic (ECG) monitoring in the presence of typical anginal pain; this phenomenon, however, has not been described before.[1–9,15]

We therefore studied the relation between anginal pain and ischemic ECG changes during ambulatory monitoring in patients with stable angina pectoris, angiographically proven coronary artery disease and positive exercise test results.

METHODS

Study group: A total of 128 men (mean age ± standard deviation 57 ± 8 years, range 32 to 81) were entered in this study. The following selection criteria had to be fulfilled: (1) presence of chronic stable angina pectoris for >3 months, (2) horizontal or downsloping ST-segment depression ≥1 mm during maximal exercise stress testing (according to age and sex), (3) angiographic evidence of >70% stenosis in at least 1 major coronary branch or >50% stenosis of the left main coronary artery, (4) normal ST segments in the electrocardiogram at rest (12 leads, CM3 and CM5 leads) and during postural changes, and (5) ≥1 episode of ischemic ECG changes or ≥1 episode of typical angina pectoris during 24-hour ambulatory monitoring. Patients receiving digitalis or antiarrhythmic drugs and patients

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with left ventricular hypertrophy, cardiomyopathy, rheumatic valve disease, bypass grafts, prior coronary angioplasty or conduction abnormalities were excluded. Thirty-two of the 128 patients (25%) received antianginal drug therapy (calcium antagonists or long-acting nitrates, or both) during the study; no patient was treated with β-blocking agents.

Cardiac catheterization: All patients underwent right- and left-sided cardiac catheterization and coronary and left ventricular angiography within 1 week of ambulatory monitoring. The degree of coronary artery lesions was estimated from several standard and half-axial projections. Stenoses with a reduction of >70% in luminal diameter (>50% in the left main coronary artery) were considered clinically relevant (visual estimate). Left ventricular ejection fraction was calculated from the end-diastolic and end-systolic volumes of cine frames obtained in a 30° right anterior oblique projection.

Ambulatory electrocardiographic monitoring: All patients were out of the hospital and were not restricted in their physical activities. Ambulatory ECG monitoring was performed using a 2-channel, direct recording system ("Tracker," Reynolds Medical). The bipolar electrodes were localized at the upper right sternal border and precordially in the CM3 and CM5 positions. The site of the exploring electrodes was occasionally modified in order to monitor the chest lead with the strongest ST-segment deviation during the exercise test. Stability of the ST segment was confirmed with the patient in a supine, upright, and left and right lateral position. The tapes were analyzed using the "Pathfinder III" system (Reynolds Medical). In addition to the computerized analysis, the tapes were scanned visually and printouts obtained from all definite and questionable episodes of ST-segment deviation. Episodes were classified as "ischemic" in the presence of ≥1 mm of ST-segment deviation 80 ms after the J point, lasting for ≥60 seconds, and separated by >60 seconds from another ischemic episode. The following parameters were determined for each ischemic episode: time and heart rate at onset of ischemia (when ST-segment depression reached 1 mm), duration of the ischemic episode, change in heart rate during the last 5 minutes before the onset of ST-segment depression, and maximal amplitude of ST-segment changes.

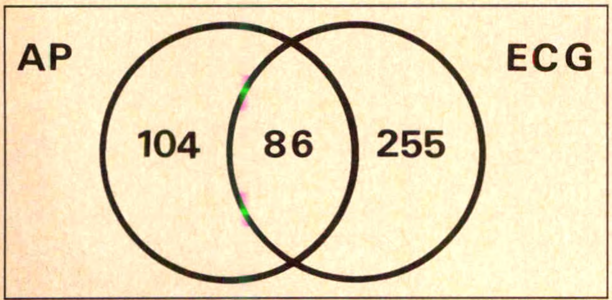

FIGURE 1. Distribution of episodes of ischemic equivalents in 128 patients: 104 episodes of anginal pain (AP) without electrocardiographic (ECG) changes during ambulatory monitoring, 86 episodes with both AP and ECG changes, and 255 episodes only with ECG changes.

Evaluation of anginal symptoms: Anginal symptoms were assessed during ambulatory ECG monitoring. The patients had to list the occurrence of all episodes of chest pain (including severity, location and radiation) or dyspnea in a diary; during these events the patients also had to push an event button. At the end of the recording period, they were interviewed regarding their symptoms either described in the diary or marked by the event button. They were also questioned about their symptoms during the exercise test. On the basis of this information, the symptoms during ambulatory monitoring were then classified as ischemic by a cardiologist, when typical chest pain with or without radiation or episodes of dyspnea comparable to similar symptoms experienced during the exercise test were present. The patients indicated a total of 242 symptomatic episodes in the diary or by the event button, or both: 52 episodes were classified as noncharacteristic for angina pectoris or its equivalents and were excluded from further analysis, and 190 symptomatic episodes were classified as anginal pain (144 episodes with mild chest pain, 28 episodes with severe chest pain and 18 episodes with dyspnea alone).

Statistics: Data are presented as mean ± 1 standard deviation. Unpaired t tests were used for continuously scaled variables; categorical variables were compared using the 2-tailed chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

Incidence of anginal episodes without ischemic electrocardiographic changes: Three different types of episodes of ischemic equivalents were observed in this study: 104 episodes with only angina pectoris, 255 episodes with only ischemic ECG changes, and 86 episodes with both anginal pain and simultaneous ischemic ECG changes (Figure 1). Among the 190 episodes with anginal symptoms (104 without and 86 with ECG changes), the severity of chest pain was mild in 144 and severe in 28 episodes; 18 episodes occurred with dyspnea alone.

From the 341 episodes with ischemic ECG changes, 86 occurred with (25%) and 255 without (75%) symptoms. Comparison between episodes with ischemic ECG changes with and without pain revealed no differences for the duration of episodes (10.3 ± 11.3 vs 11.0 ± 11.0 minutes; difference not significant [NS]), extent of ST-segment depression (2.2 ± 0.9 vs 2.1 ± 0.8 mm; NS), and heart rate at the onset of ST-segment depression (96 ± 19 vs 100 ± 14 beats/min; NS). The circadian distribution was also similar for ischemic ECG episodes with or without angina pectoris and for the 104 anginal episodes without ischemic ECG changes (Figure 2); most episodes of all types occurred during the morning or the afternoon hours. An increase in heart rate of ≥10 beats/min before the onset of ST depression occurred in 209 episodes with asymptomatic (82%) and in 70 episodes with symptomatic (81%) ECG changes; 82 of the anginal episodes without ECG changes (79%) were related to periods of increased heart rate.

Patients with anginal episodes without ischemic electrocardiographic changes: An individual patient could exhibit only 1 type of episode or a combination of

TABLE I Number of Patients With Episodes of Angina Pectoris Without Ischemic Electrocardiographic Changes, Episodes With Both Angina Pectoris and Electrocardiographic Changes During Ambulatory Monitoring, and Episodes With Only Ischemic Electrocardiographic Changes

	Episodes with		
	AP	AP + ECG	ECG
Group A (n = 44)			
n = 29 (23%)	+	0	0
n = 3 (2%)	+	+	0
n = 6 (5%)	+	+	+
n = 6 (5%)	+	0	+
Group B (n = 84)			
n = 53 (41%)	0	0	+
n = 24 (19%)	0	+	+
n = 7 (5%)	0	+	0

AP = angina pectoris without electrocardiographic changes; AP + ECG = angina pectoris with electrocardiographic changes; ECG = electrocardiographic changes without angina pectoris.

TABLE II Comparison of Baseline Clinical Characteristics, Angiographic Findings and Exercise Testing Data Between Groups A and B

	Group A	Group B
No. of patients	44	84
Age (years)	58 ± 7	57 ± 8
Patients taking antiischemic therapy	14 (32%)	18 (21%)
Calcium antagonists	2 (5%)	2 (2%)
Long-acting nitrates	2 (5%)	3 (4%)
Calcium antagonist + long-acting nitrates	10 (23%)	13 (15%)
Cardiac catheterization		
No. of coronary arteries narrowed		
1	25 (57%)	30 (36%)
2	17 (36%)	22 (26%)
3	5 (11%)	22 (26%)
LM	1 (2%)	6 (7%)
Left ventricular ejection fraction (%)	65 ± 11	64 ± 10
Exercise testing		
Onset of ischemia		
Heart rate (beats/min)	115 ± 22	110 ± 16
Duration (min)	5.4 ± 2.4	4.8 ± 2.0
No of pts. with angina pectoris	37 (84%)	73 (87%)
Time to onset of angina pectoris (min)	6.1 ± 2.9	5.5 ± 2.0
Maximal exercise		
Heart rate (beats/min)	125 ± 25	127 ± 19
Duration (min)	7.2 ± 1.9	6.8 ± 2.1
ST depression (mm)	1.9 ± 0.9*	2.4 ± 0.8*

* $p < 0.05$.
All values are mean ±1 standard deviation.
LM = left main coronary artery.

different types of episodes. Altogether, 7 different combinations of the 3 types of episodes were possible and also observed (Figure 3 and Table I).

Episodes of anginal pain without simultaneous ECG changes were detected in 44 of the 128 patients (34%) (group A) (Table I, Figure 3); 29 patients in this group only had episodes of angina and had no ischemic ECG changes during ambulatory monitoring. The other 15 patients in group A also had anginal episodes without ECG changes but had episodes with ischemic ECG changes (with or without anginal pain) as well. In 84 patients (66%) (group B), episodes of anginal pain without ischemic ECG changes were not seen (Figure 3, Table I): 53 patients had only asymptomatic ECG changes, 24 patients had both symptomatic and asymptomatic episodes with ECG changes, and 7 patients had only symptomatic ECG changes.

Group A and B patients had no significant differences in the prevalence of antianginal therapy, in findings during cardiac catheterization (number of coronary arteries narrowed and left ventricular ejection fraction), and in exercise testing data (heart rate and duration of exercise at the onset of ischemia and at maximal exercise, and time to onset of angina pectoris) (Table II). However, maximal amplitude of ST-segment depression during stress testing was significantly greater in group B patients.

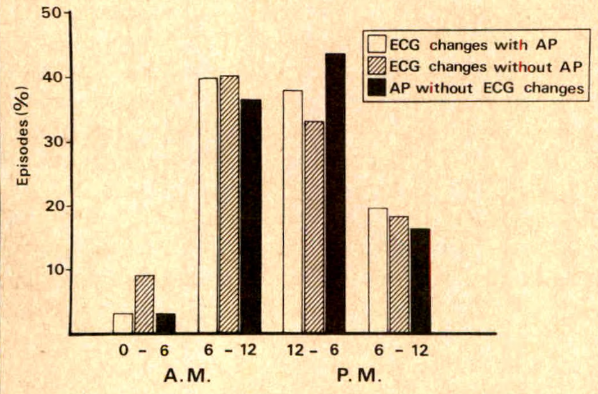

FIGURE 2. Circadian distribution of ischemic equivalents: 86 episodes of electrocardiographic (ECG) changes with angina pectoris (AP) *(open bars)*, 255 episodes of ECG changes without AP *(hatched bars)*, and 104 episodes of AP without ECG changes *(closed bars)*. The circadian distribution was similar in all 3 types of episodes; most episodes occurred during the morning and the afternoon hours.

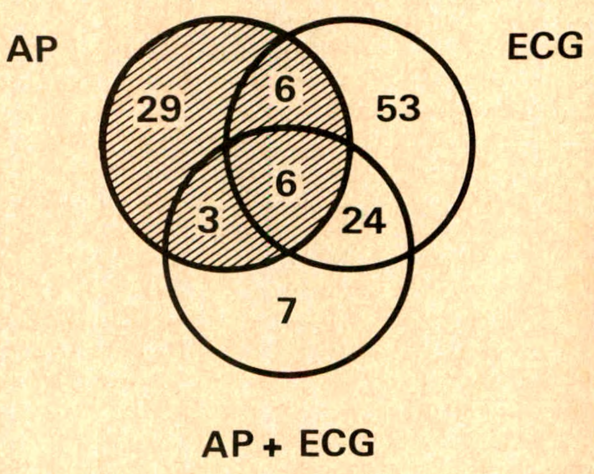

FIGURE 3. Distribution of patients with regard to the combinations of the 3 types of ischemic equivalents: episodes with only angina pectoris (AP), episodes with only ischemic electrocardiographic (ECG) changes and episodes with both AP and ECG changes (AP + ECG) during ambulatory monitoring. Patients can have 7 different combinations of the episodes (see Table I). Anginal episodes without ischemic ECG changes were present in group A *(hatched area)*; anginal episodes with ischemic ECG changes *(open area)* were present in group B.

DISCUSSION

The purpose of this study was to analyze the incidence of episodes of angina pectoris unaccompanied by ischemic ECG changes during ambulatory monitoring in patients with stable angina pectoris, angiographically proven coronary artery disease and positive exercise test results. In particular, the question is addressed whether anginal pain without ECG changes during ambulatory monitoring can be accepted as an equivalent of myocardial ischemia.

In our study, 15 of the 128 patients (12%) had both episodes of ischemic ECG changes and anginal pain without ECG changes during the same 24-hour recording period. We assumed that these patients were more likely to have anginal episodes without ECG changes, i.e., "electrocardiographically silent" myocardial ischemia.[10] Whether one can assume that these episodes also are ischemic in origin in the 29 patients having only anginal attacks without ECG changes during ambulatory monitoring remains questionable, since one cannot exclude the fact that chest pain in these patients represents "false-positive angina symptomatic." [10]

Myocardial ischemia without electrocardiographic changes: Several studies have demonstrated that equivalents of myocardial ischemia might be apparent in the thallium stress scintigram,[10,11] radionuclide ventriculogram[12] or positron emission tomogram[13] in the absence of ischemic ECG changes. These observations indicate the relative insensitivity of the electrocardiogram in detecting myocardial ischemia. This was also documented during exercise testing[14,16] and during coronary artery balloon dilatation[17] when hemodynamic changes (increase in end-diastolic pressure) occurred much earlier than ECG alterations. However, electrocardiographically silent myocardial ischemia might carry important prognostic information, because in patients with negative ECG exercise test results, the incidence of adverse clinical events is significantly higher in those with a positive thallium stress scintigram than in those with a normal thallium test.[10,18] Furthermore, Weiner et al[19] found that 7-year survival was similar for patients with typical ST-segment depression during exercise testing and for those with angina but no ischemic ST depression; this also indicates that angina during exercise is a critical event when associated with coronary artery disease.

The present study has shown that typical anginal pain in the absence of ischemic ECG changes during ambulatory monitoring may represent an equivalent of ischemia in certain patients. Anginal pain without ECG changes is a frequent finding during ambulatory monitoring; however, it may only be accepted as an equivalent of ischemia in patients whose diagnosis of coronary artery disease and myocardial ischemia was proven by other methods and whose ischemic ECG changes occurred during other periods of ambulatory monitoring. In such patients one has to assume that the total amount of myocardial ischemia[4] is not only represented by the number of symptomatic and asymptomatic ECG episodes during ambulatory monitoring, but also by episodes of angina without ECG changes.

This concept is supported by the observation in the present study, that patients exhibiting anginal episodes unaccompanied by ECG changes did not differ from patients with ischemic ECG changes with regard to the angiographic extent of coronary artery disease or exercise test performance. However, maximal ST depression during exercise was significantly lower in patients with anginal episodes without ECG changes during ambulatory monitoring. This finding suggests that these patients may represent a special group whose signs of myocardial ischemia are less pronounced in the electrocardiogram. Our observation is further supported by the fact that the circadian distribution was similar for anginal episodes without and for ischemic episodes with ECG changes; all types of episodes predominantly occurred during the morning and afternoon hours. In addition, most anginal episodes without as well as those with ECG changes were accompanied by increases in heart rate.

Study limitations: Assessment of anginal symptoms during ambulatory monitoring is influenced by patient compliance; however, this problem is inherent in all investigations measuring subjective symptoms under out-of-hospital conditions. Importantly, the lack of ECG signs of ischemia during ambulatory monitoring in the presence of typical anginal pain could be caused by technical problems of this method.[20,21] The small number of recording leads (usually 2 to 3 leads) reduces the sensitivity in detecting ischemic ECG changes when compared with multiple lead devices.[22,23] In addition, inferior ischemia may have been missed by electrodes located in the anterior chest wall in the position of CM3 and CM5.[24] Finally, ischemic electrocardiographic changes could have been overlooked with this method because of a lead placement on the chest wall in a "nonischemic area." [22] In our study the lead positions CM3 and CM5 have been used according to a previous report[25] demonstrating a good correlation with a standard 12-lead electrocardiogram recorded simultaneously during ambulatory monitoring. In addition, an exercise test was performed before ambulatory monitoring in all patients and, if necessary, the location of the lead was modified in order to simulate the lead showing the strongest ST deviation during the exercise test.

Nevertheless, it appears reasonable that technical problems in ambulatory monitoring contribute to the lack of ECG signs of ischemia during typical angina pectoris in some of our patients. However, this does not invalidate the need for careful monitoring of anginal episodes without ECG changes during ambulatory monitoring. In patients having episodes with ischemic ECG changes during ambulatory monitoring, angina without ECG changes should be included when the total amount of myocardial ischemia[4] is estimated.

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Dependence of Doppler Echocardiographic Transmitral Early Peak Velocity on Left Ventricular Systolic Function in Coronary Artery Disease

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The influence of systolic function on pulsed Doppler echocardiographic transmitral flow velocity patterns was assessed before and after postextrasystolic (PES) potentiation in 12 normal subjects (control group) and in 25 patients with previous healed myocardial infarction (MI) group. Simultaneous high-fidelity left ventricular pressure measurements were performed in all patients. A programmed single-coupled right ventricular extrasystole was induced during echocardiographic and subsequent cineangiocardiographic recordings. Adequate angiograms for volumetric analysis in both baseline and PES beats were obtained in 23 patients (7 in the control group and 16 in the MI group).

PES potentiation of contraction was more pronounced in the MI group than in the control group. PES changes in ejection fraction, stroke volume and end-systolic volume were significantly greater in the MI group than in the control group (11 vs 5%, $p < 0.005$; 15 vs 5 ml/m^2, $p < 0.005$; and −13 vs −4 ml/m^2, $p < 0.01$, respectively). In contrast, PES potentiation prolonged the time constants of left ventricular pressure decline derived from exponential curve fits with a zero (Tw) and non-zero (Tb) asymptote pressure in the MI group to the same extent as in the control group (4 vs 5 ms, difference not significant [NS], and 9 vs 11 ms, NS, respectively). In the PES beat, peak E velocity remained unaltered (48 vs 49 cm/s, NS) in the control group, whereas it increased significantly ($p < 0.0001$) from 47 to 51 cm/s in the MI group. In contrast, peak E velocity normalized to time velocity integral during diastole, which is equivalent to volumetric peak filling rate normalized to stroke volume (SV), decreased after PES potentiation in both control and MI groups (from 5.2 to 4.7 SV/s, $p < 0.005$ and from 5.5 to 5.2 SV/s, $p < 0.005$, respectively).

In conclusion, despite a prolonged relaxation, PES potentiation of contraction maintained peak E-wave velocity in the control subjects and enhanced it in patients with MI. Early diastolic filling is strongly affected by systolic function. Thus, the influence of the preceding contraction should be accounted for in the Doppler echocardiographic assessment of early diastolic filling dynamics.

(Am J Cardiol 1991;67:470–478)

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Previous experimental and clinical studies have investigated the relation of an early diastolic filling pattern to left ventricular loading conditions,[1–6] relaxation[4,5,7,8] and chamber properties.[8,9] The decreases in filling pressure, the rate of left ventricular pressure decline, or diastolic compliance cause decelerated early diastolic filling and vice versa. On the other hand, Hammermeister et al[10] demonstrated, using contrast angiography, a strong correlation between stroke volume and early diastolic peak filling rate in various heart diseases. Recently, Zile et al[11] demonstrated an inverse relation between early diastolic filling rate and end-systolic volume, i.e., an index of elastic recoil. However, few studies have addressed the dependence of Doppler early diastolic velocity indexes on preceding systolic function in the clinical setting. Blaustein et al and others[12–14] reported that postextrasystolic (PES) potentiation is associated with an unaltered or delayed isovolumic relaxation (dissociation of contraction and relaxation). Thus, PES potentiation is an interesting phenomenon, allowing assessment of the separate effects of contraction and relaxation on early diastolic filling. The purpose of the present study is to clarify the effects of systolic ejection performance on pulsed Doppler transmitral flow velocity pattern before and after PES potentiation in control subjects and in patients with previous myocardial infarction (MI).

METHODS

Patients: This study was performed in 37 patients during cardiac catheterization. Twenty-five patients (19 men and 6 women [mean age 59 years, range 40 to 77]) had coronary artery disease (>50% diameter narrowing) and myocardial infarction (MI group); 18 had isolated anterior, 6 had inferior and 1 had combined ante-

rior and inferior infarction. Twelve patients (6 men and 6 women [mean age 53 years, range 38 to 76]), who complained of chest pain but had no cardiovascular disease, served as the control group. All patients were normotensive and patients who had aortic or mitral regurgitation on their Doppler echocardiograms or contrast left ventriculograms, or both, were excluded from the study. Written informed consent was obtained from all patients.

Cardiac catheterization: Patients underwent right- and left-sided cardiac catheterization in the fasting state. Premedication consisted of 10 mg of diazepam administered orally 1 hour before the study. Among 25 patients with previous MI, 13 were receiving long-term medication with calcium antagonists and 17 patients were taking long-acting nitrates. No patients were receiving β blockers, digitalis or diuretics. All these medications had been withdrawn $\geq$24 hours before the study.

After routine right-sided cardiac catheterization, an 8Fr Miller angiocardiographic micromanometer was introduced into the left ventricle through the right femoral artery. A pacing catheter was inserted into the right ventricle through the right femoral vein. The micromanometer pressure tracing was superimposed on the conventional pressure tracing, which was obtained from the side lumen of the catheter with the use of a fluid-filled system. Pressures and the first derivative of pressure (dP/dt) were recorded at a paper speed of 200 mm/s (Fukuda Denshi, MIC-9800).

After placement of the catheters, pulsed Doppler echocardiography was performed with an Aloka SSD-860 equipped with a 3.0-MHz transducer. For Doppler measurements of left ventricular inflow velocity curve an apical 4-chamber view was obtained. The Doppler beam was aligned so as to be as parallel as possible to the blood flow vector. The sample volume was positioned at the level of the mitral anulus. Because the Doppler beam was almost parallel to the presumed flow, angle correction was not made. The mitral inflow velocity and simultaneous high-fidelity left ventricular pressure curves were recorded at a paper speed of 50 and 100 mm/s. During Doppler recording, extrasystoles were induced by a programmed electrical stimulus generator (Fukuda Denshi, DC-03) attached to the pacing catheter in the right ventricle. The coupling intervals were held constant during echocardiographic and cineangiocardiographic evaluations. The mean coupling interval was 417 ms (range 400 to 500) in the control group and 422 ms in the MI group (range 350 to 550).

Immediately after the Doppler echocardiographic recordings, simultaneous biplane left ventricular cineangiocardiography was performed in the 30° right anterior oblique and 60° left anterior oblique projections with nonionic contrast medium injected at a rate of 12 ml/s. Filming rate was 60 frames/s. Left ventricular pressure, dP/dt and a peripheral lead of the standard electrocardiogram were recorded at a paper speed of 200 mm/s. Each angiographic frame had a digital time that corresponded to time marks on the pressure recordings. During left ventriculography, an extrasystole was induced immediately after the second well-opacified beat in the same fashion as in the Doppler recordings. All patients with MI had left ventricular regional wall motion abnormalities corresponding to the sites of MI on their control angiograms. Finally, coronary arteriography was performed by the Judkins technique.

Pressures and flow velocity data analysis: All patients were in sinus rhythm and the duration of QRS complex did not exceed 0.11 second. All values obtained from simultaneous left ventricular pressure and transmitral Doppler recording were calculated as an average of $\geq$5 cardiac cycles. Left ventricular pressure and transmitral flow velocity were digitized for an entire cardiac cycle by an electronic digitizer (Graftec KD-3200) interfaced to a computer. The sampling rate for pressure and dP/dt value was 3.0 ms. For quantitative assessment of transmitral flow velocity, the following measurements were calculated: (1) peak velocities of the early filling (E; cm/s) and atrial contraction (A; cm/s) waves; (2) the ratio of peak early filling wave velocity to peak atrial contraction wave velocity (E/A); (3) time velocity integral (i.e., area under the velocity curves) during diastole (TVI; cm); (4) percent increase of time velocity integral during the first half of diastole (%TVI1); (5) peak early filling wave velocity normalized to time velocity integral during diastole (E/TVI). When the mitral anulus cross-sectional area (CSA; cm^2) is assumed constant, the product of E and CSA represents volumetric peak filling rate (PFR; ml/s) (E $\times$ CSA = PFR). Likewise, the product of TVI and CSA is equal to mitral stroke volume (SV; ml) (TVI $\times$ CSA = SV). From these equations, it can be drawn that E/TVI is equivalent to PFR/SV. This concept was proposed by Bowman et al[15] and the excellent correlation between this normalized Doppler echocardiographic and radionuclide angiographic volumetric peak filling rates was demonstrated by these investigators.

In this study, the left ventricular isovolumic relaxation period was defined as the interval from maximum negative dP/dt to the beginning of E wave. The time constant of left ventricular isovolumic pressure decay was determined by 2 approaches, using exponential function as follows: (1) $P = P_0\, e^{(-1/Tw)t}$, and (2) $P = (P_0 - P_A)\, e^{(-1/Tb)t} + P_A$ in which pressure was assumed to decay to a zero[16] and variable asymptote pressure (P_A),[17,18] respectively. Tw was determined as the negative reciprocal of the linear relation between ln P versus time (t) by least-squares regression analysis. The mean correlation coefficient was −0.995 (range −0.988 to −0.998) during baseline beat and −0.995 (range −0.992 to −0.999) after PES potentiation in the control group; it was −0.997 (range −0.989 to −0.999) during baseline beat and −0.997 (range −0.991 to −0.999) after PES potentiation in the MI group. Tb was determined as that between ln ($P - P_A$) versus t by an iteration procedure[17,18] (Figure 1). This approach also provided an excellent mean correlation coefficient. It was −0.999 (range −0.997 to −0.999) during the baseline beat and −0.999 (range −0.998 to −0.999) after PES potentiation in the control group. The coefficient was −0.999 (range −0.997 to −0.999) during the baseline

beat and −0.999 (range −0.999 to −0.999) after PES potentiation in the MI group.

Left ventricular pressure at atrioventricular pressure crossover is another important determinant of early diastolic transmitral pressure gradient.[19] Because atrial pressure was not directly determined, we measured left ventricular pressure at the beginning of the early diastolic wave forms. This is termed mitral valve opening pressure and is used as an index of left atrial driving pressure responsible for mitral valve opening.

Angiocardiographic data analysis: Five patients in the control group and 9 patients in the MI group were excluded from the volume analysis because the opacification of the left ventricle was not satisfactory especially in the PES beat. Left ventricular volume was calculated by the area-length method. In this study, end-systole was defined as the angiographically determined point of aortic closure and end-diastole was defined as the beginning of the rapid increase of left ventricular pressure immediately after the onset of the QRS complex. End-diastolic, end-systolic and stroke volume indexes, and ejection fraction were calculated in the standard fashion. In addition, the time interval from mitral valve opening to end-diastole was divided into a first and second half. Volume increases during each period (V_1 and V_2) and percent volume increase during the first half of diastole ($\%V_1$) were determined.

Statistics: Comparisons of hemodynamics and angiographic parameters between the baseline and PES beats were performed by Student's paired *t* test. Comparisons between control and MI groups were determined by an unpaired *t* test. Differences were considered significant at $p < 0.05$. Data in the tables and figures are presented as mean ± 1 standard deviation.

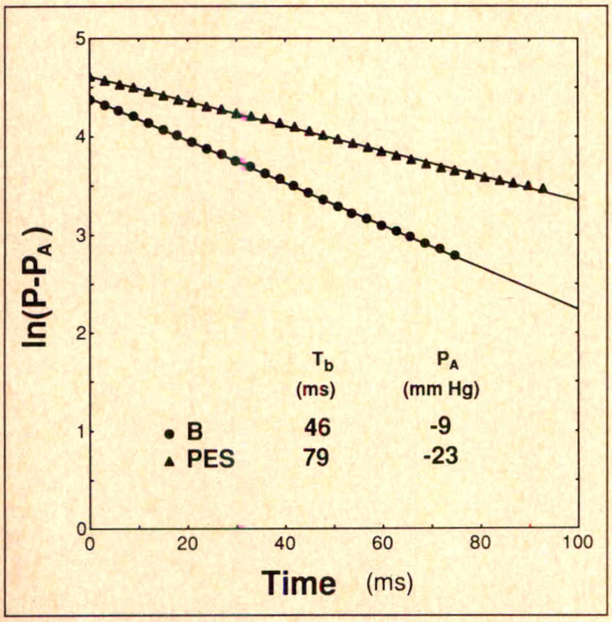

FIGURE 1. Representative semilogarithmic plots of left ventricular pressure minus asymptote pressure [ln(P − P_A)] versus time in a normal subject. The time constants (T_b) of relaxation are determined as the negative reciprocal of the slope of the linear relation between ln(P − P_A) and time. In this case, the time constant increased from 46 to 79 ms and asymptote pressure decreased from −9 to −23 mm Hg after the postextrasystolic (PES) beat. B = baseline.

RESULTS

Left ventricular pressure and angiographic parameters (Tables I and II): In the PES beat, left ventricular peak systolic pressure did not change but end-diastolic pressure increased slightly in both control and MI groups. Mitral valve opening pressure remained unaltered in the 2 patient groups. Left ventricular minimum pressure did not change in the control group; it decreased slightly but significantly in the MI group. End-diastolic volume did not change in the PES beat in both groups. PES potentiation increased maximum positive dP/dt in the control and MI groups. PES potentiation of ejection performance was more pronounced in the MI group than in the control group. The changes in ejection fraction, stroke volume and end-systolic volume were greater in the MI group than in the control group (11 vs 5%, $p < 0.005$; 15 vs 5 ml/m^2, $p < 0.005$; and −13 vs −4 ml/m^2, $p < 0.01$, respectively) (Figure 2).

PES potentiation impaired left ventricular relaxation in both groups. Maximum negative dP/dt decreased and both Tw and Tb increased in the control and MI groups. The changes in maximum negative dP/dt, Tw and Tb in PES beat were not significantly different between the 2 groups. V1 increased after PES potentiation in both groups. V2 did not change in the PES beat in control patients but increased slightly in patients with MI. Percent V1 remained unchanged in the PES beat in the controls; it increased slightly but not significantly in the MI group.

Doppler echocardiographic measurements (Table III, Figures 3 and 4): PES potentiation did not change peak E-wave velocity significantly in control patients, whereas it enhanced the velocity slightly but significantly in the MI group. Peak A-wave velocity increased slightly after PES potentiation in both control and MI groups. PES potentiation increased TVI in the control and MI groups in association with a decrease in E/TVI. The E/A ratio did not change significantly after PES potentiation in both control and MI groups. Percent TVI1 did not change significantly after PES potentiation in the control patients; it increased slightly in patients with MI.

DISCUSSION

Postextrasystolic early diastolic filling: The present study revealed that left ventricular contraction was potentiated but relaxation was impaired in the PES beat in the control and MI groups. PES potentiation of contraction was more pronounced in the MI group than in the control group. On the other hand, impairment of left ventricular relaxation in the MI group was similar to that in the control group. In this study, we determined peak E-wave velocity and its normalization to TVI to distinguish the effect of left ventricular contraction from that of relaxation on early diastolic filling. There were discrepancies in the response to PES potentiation between these absolute and relative early diastolic Doppler peak velocity indexes. In the PES beat,

peak E-wave velocity remained unaltered in the control group, whereas it was enhanced in association with more pronounced contraction in the MI group. In contrast, E/TVI was reduced after PES potentiation in both control and MI groups. E/TVI is theoretically equivalent to volumetric peak filling rate normalized to mitral stroke volume[15] and thus is an index eliminating the potential effect of systolic ejection performance on early diastolic peak filling rate. Its reduction after PES potentiation may reflect, at least in part, slowed left ventricular pressure decline in these 2 groups. Our results indicate that left ventricular contraction and relaxation contributed profoundly to determining peak E-wave velocity in the PES beat in our patients. In the control group, the effect of left ventricular contraction on early diastolic peak filling rate might be counterbal-

TABLE I Left Ventricular Pressure and Derived Data in 37 Patients

Pt. No.	HR (beats/min)	LVEDP (mm Hg)		LVSP (mm Hg)		MVOP (mm Hg)		LVmin (mm Hg)		dP/dt max (mm Hg/s)		dP/dt min (mm Hg/s)		Tw (ms)		Tb (ms)	
	B	B	PES	B	PES	B	PES	B	PES	B	PES	B	PES	B	PES	B	PES
Control Patients																	
1	55	9	15	152	135	9	6	2	3	1,631	1,967	−1,422	−1,132	48	53	68	63
2	68	15	17	142	108	8	12	3	5	1,474	1,769	−1,708	−888	39	45	43	63
3	69	7	7	152	145	6	6	4	3	1,309	1,648	−1,639	−1,492	39	41	53	67
4	85	12	11	157	166	11	10	3	4	2,266	2,775	−1,631	−1,527	34	37	64	80
5	66	17	17	158	151	15	15	4	4	1,798	2,347	−2,041	−1,727	40	52	51	56
6	67	11	10	159	150	12	12	3	3	1,592	1,936	−1,396	−1,317	39	44	60	81
7	71	11	12	118	106	9	10	1	1	1,386	1,524	−1,340	−1,168	34	39	50	55
8	58	3	6	117	116	6	11	1	1	1,180	1,239	−1,272	−1,071	36	44	46	66
9	52	15	16	150	160	14	14	6	7	1,483	1,617	−1,327	−1,349	45	47	59	65
10	71	7	8	107	102	6	8	1	3	1,044	1,180	−1,305	−1,010	29	38	42	77
11	86	7	10	147	125	9	7	1	2	2,414	2,637	−1,953	−1,537	27	30	42	38
12	61	11	12	120	130	10	6	4	2	1,325	1,552	−1,360	−1,669	38	38	42	44
Patients with Myocardial Infarction																	
1	68	14	14	116	101	12	10	5	4	1,302	1,661	−1,233	−974	39	44	50	59
2	68	14	15	127	121	13	14	4	6	1,300	1,524	−1,184	−1,061	44	50	58	64
3	72	10	11	133	140	7	5	4	2	1,385	1,467	−1,271	−1,210	37	39	41	54
4	65	28	27	112	109	30	24	8	6	1,072	1,148	−967	−955	55	54	112	96
5	44	19	21	124	115	24	25	6	4	1,276	1,489	−1,218	−857	58	68	62	93
6	71	11	17	139	146	7	7	1	1	1,517	1,516	−1,460	−1,463	35	39	52	54
7	75	12	16	148	149	14	12	9	6	1,513	1,849	−1,442	−1,327	45	47	47	55
8	62	7	11	93	97	11	11	3	1	1,113	1,247	−876	−869	42	45	57	73
9	75	17	16	134	143	17	9	5	2	1,620	2,233	−1,441	−1,508	38	35	55	58
10	65	22	23	118	125	24	19	7	6	1,000	1,043	−996	−1,095	56	56	85	90
11	77	10	13	127	102	11	18	4	4	1,692	2,030	−1,579	−1,024	39	50	40	42
12	86	30	27	99	105	25	29	10	10	835	1,085	−918	−846	52	53	112	158
13	57	17	18	159	123	13	22	4	5	950	1,424	−1,820	−1,741	46	54	59	74
14	77	9	10	122	139	6	6	1	2	1,190	1,580	−1,745	−1,586	30	34	51	55
15	60	16	17	128	120	13	12	6	7	1,477	1,723	−1,600	−1,354	46	50	49	61
16	90	32	30	124	120	13	13	5	3	1,007	1,125	−1,095	−1,081	35	41	50	53
17	76	12	18	145	133	11	21	7	6	1,344	1,381	−1,475	−1,407	40	45	69	60
18	65	12	13	146	143	11	14	9	5	1,195	1,208	−1,364	−1,253	42	44	52	62
19	54	31	30	91	93	27	24	10	11	848	930	−614	−552	74	83	108	116
20	72	17	17	113	102	20	18	10	7	1,102	1,259	−934	−800	55	59	71	83
21	65	18	18	131	128	21	25	4	2	1,457	1,879	−1,268	−1,129	46	52	68	80
22	81	10	9	122	116	5	5	3	2	1,560	1,647	−1,284	−1,012	35	41	48	61
23	66	16	18	154	148	20	11	9	8	1,339	1,335	−1,311	−1,179	54	52	66	68
24	49	16	18	167	133	15	10	2	1	1,849	2,080	−1,511	−1,067	41	47	71	95
25	70	19	18	146	155	16	16	9	6	1,321	1,569	−1,404	−1,239	53	54	61	63
Control Patients (n = 12)																	
Mean	67	10	12	140	133	9	10	3	3	1,575	1,849	−1,533	−1,324	37	42	52	63
±SD	±10	±4	±4	±18	±21	±3	±3	±1	±2	±394	±488	±249	±260	±6	±6	±9	±13
p value		<0.05		NS		NS		NS		<0.0001		<0.05		<0.0005		<0.01	
Patients with Myocardial Infarction (n = 25)																	
Mean	68	17	18	129	124	15	15	6	4	1,290	1,497	−1,280	−1,144	45	49	64	73
±SD	±10	±7	±6	±19	±18	±7	±7	±3	±3	±257	±332	±282	±268	±10	±10	±20	±24
p value		<0.05		NS		NS		<0.005		<0.0001		<0.0001		<0.0001		<0.001	

Data are presented in the baseline (B) and postextrasystolic (PES) states in the control subjects and patients with myocardial infarction.
B = baseline; dP/dtmax, dP/dtmin = maximal positive dP/dt and negative dP/dt; HR = heart rate; LVEDP, LVmin, LVSP = left ventricular end-diastolic, minimum and peak systolic pressures; MVOP = mitral valve opening pressure; NS = not significant; PES = postextrasystolic; Tb, Tw = time constants of isovolumic left ventricular pressure decay with non-zero and zero asymptote pressures.

TABLE II Angiographic Data in 23 Patients

Pt. No.	EDV (ml/m²) B	EDV (ml/m²) PES	ESV (ml/m²) B	ESV (ml/m²) PES	EF (%) B	EF (%) PES	SV (ml/m²) B	SV (ml/m²) PES	V1 (ml/m²) B	V1 (ml/m²) PES	V2 (ml/m²) B	V2 (ml/m²) PES	%V1 B	%V1 PES
Control Patients														
1	99	101	29	26	71	74	71	75	39	44	28	28	59	61
2	80	82	14	13	82	84	66	69	34	36	30	27	53	57
3	112	107	43	32	61	70	68	75	43	51	24	22	64	70
4	76	81	23	20	70	75	54	60	36	37	18	22	66	55
5	108	107	28	24	74	78	80	83	61	76	13	4	82	95
6	75	78	23	21	69	73	52	57	38	41	13	14	87	74
7	75	76	24	20	68	74	52	56	31	36	18	20	62	64
Patients with Myocardial Infarction														
1	95	96	47	31	50	68	48	66	22	45	10	13	70	77
2	114	114	55	45	51	61	58	69	33	44	20	22	63	67
3	101	102	51	38	50	63	50	64	13	35	26	25	33	58
4	157	159	91	83	42	48	66	76	51	65	6	6	89	92
5	134	135	73	71	46	48	61	64	43	52	12	7	80	89
6	110	116	53	43	52	63	57	73	35	38	21	29	63	57
7	96	95	63	51	34	46	32	44	21	24	10	18	67	58
8	124	117	74	57	40	52	50	61	35	38	17	21	67	65
9	128	126	61	45	52	64	67	81	46	52	14	25	76	68
10	153	161	84	76	45	53	69	85	54	65	12	14	82	82
11	98	100	44	36	56	64	55	64	33	31	21	31	61	50
12	215	224	162	135	24	40	52	89	24	44	21	39	52	54
13	111	118	44	33	60	72	67	85	50	63	19	21	73	75
14	82	87	36	33	56	62	46	54	19	23	21	24	48	50
15	139	143	72	59	48	59	68	84	35	61	24	24	59	72
16	131	127	91	63	31	50	40	64	9	38	29	22	24	63
Control Patients (n = 7)														
Mean	90	90	26	22	71	75	63	68	40	46	21	20	68	68
±SD	±15	±13	±8	±6	±6	±4	±10	±10	±9	±13	±6	±8	±12	±13
p value	NS		<0.025		<0.005		<0.005		<0.025		NS		NS	
Patients with Myocardial Infarction (n = 16)														
Mean	124	126	69	56	46	57	55	70	33	45	18	21	63	67
±SD	±31	±33	±29	±26	±9	±9	±10	±12	±13	±13	±6	±8	±17	±13
p value	NS		<0.0001		<0.0001		<0.0001		<0.0001		<0.05		NS	

Data are presented in the baseline (B) state and postextrasystolic (PES) states in control subjects and patients with myocardial infarction.
B = baseline; EDV, ESV = end-diastolic and end-systolic volume; EF = ejection fraction; NS = not significant; PES = postextrasystolic; SV = stroke volume; V1, V2 = volume increase during the first and the second half of diastole; %V1 = percent volume increase during the first half of diastole.

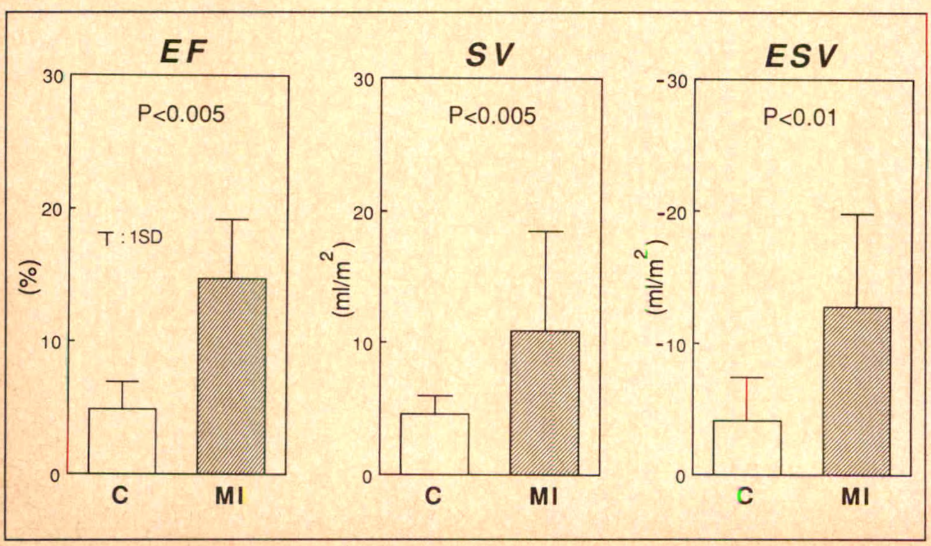

FIGURE 2. Angiographic changes in left ventricular ejection fraction (EF), stroke volume (SV) and end-systolic volume (ESV) after postextrasystolic potentiation in the controls (C) and patients with myocardial infarction (MI). SD = standard deviation.

anced by that of relaxation in the PES beat. However, in the MI group, the effect of contraction exceeded that of relaxation, resulting in an accelerated early diastolic peak filling velocity. In this study, there were discrepancies in the PES responses of early diastolic filling parameters. E/TVI was lower in the PES beat, whereas %V1 and %TVI1 did not change in the controls and increased slightly in the MI group. The time of occurrence of the peak E wave is close to the moment of isovolumic relaxation and thus the influence of delayed PES relaxation on E/TVI might be more marked than on %V1 or %TVI1.

Using contrast cineangiocardiography or Doppler echocardiography, several investigators have assessed

TABLE III Doppler Echocardiographic Mitral Flow Indexes in 37 Patients

Pt. No.	Peak E (cm/s) B	Peak E (cm/s) PES	Peak A (cm/s) B	Peak A (cm/s) PES	E/A B	E/A PES	TVI (cm) B	TVI (cm) PES	%TVI1 (%) B	%TVI1 (%) PES	E/TVI (SV/s) B	E/TVI (SV/s) PES
Control Patients												
1	37	35	38	41	0.97	0.85	6.7	7.0	65	60	5.5	5.0
2	37	40	72	74	0.51	0.53	10.9	11.9	47	50	3.4	3.3
3	28	30	59	61	0.48	0.48	8.4	9.0	43	42	3.3	3.3
4	51	49	93	93	0.55	0.53	12.2	13.2	41	42	4.2	3.7
5	51	52	44	43	1.17	1.20	8.3	10.2	64	67	6.1	5.1
6	48	54	52	59	0.92	0.91	9.9	11.8	60	60	4.9	4.5
7	60	62	52	50	1.16	1.25	10.3	10.7	68	69	5.8	5.8
8	40	41	41	41	0.98	1.00	8.7	10.2	59	61	4.6	4.0
9	46	42	58	59	0.79	0.71	8.5	10.2	58	60	5.4	4.1
10	48	51	33	35	1.44	1.46	8.5	9.3	69	70	5.6	5.5
11	75	73	70	74	1.06	0.98	11.9	13.4	57	58	6.2	5.4
12	62	65	40	40	1.56	1.63	8.5	10.6	72	77	7.3	6.1
Patients with Myocardial Infarction												
1	39	38	46	41	0.85	0.93	8.6	8.1	57	61	4.5	4.7
2	31	35	47	44	0.66	0.80	6.6	7.8	56	59	4.7	4.5
3	23	25	35	41	0.66	0.60	4.9	6.3	43	44	4.8	3.9
4	54	56	37	39	1.46	1.44	7.1	9.0	73	76	7.6	6.2
5	59	66	31	33	1.90	2.00	8.7	9.7	78	80	6.8	6.8
6	57	59	52	55	1.09	1.07	7.9	10.4	62	65	7.2	5.6
7	40	41	44	45	0.91	0.91	7.1	7.7	53	57	5.6	5.4
8	60	64	57	52	1.05	1.24	13.4	13.6	65	71	4.5	4.7
9	55	70	45	49	1.22	1.44	9.2	12.5	67	71	6.0	5.6
10	35	40	25	30	1.42	1.32	5.3	6.5	73	73	6.7	6.1
11	75	79	62	63	1.22	1.25	12.8	14.5	63	65	5.9	5.5
12	68	70	41	49	1.65	1.42	9.2	11.2	69	67	7.4	6.2
13	48	53	38	38	1.28	1.40	8.0	8.9	72	74	6.0	5.9
14	34	41	50	63	0.68	0.66	7.4	9.3	57	60	4.7	4.4
15	38	47	64	62	0.59	0.76	11.0	12.2	51	58	3.4	3.9
16	33	35	44	48	0.74	0.73	5.0	6.5	56	56	6.6	5.4
17	51	53	55	57	0.92	0.93	9.9	10.4	59	59	5.1	5.1
18	25	28	50	50	0.50	0.56	7.0	7.6	48	54	3.6	3.7
19	48	54	52	53	0.93	1.02	10.6	12.9	72	73	4.6	4.2
20	67	72	55	65	1.22	1.11	11.5	13.3	60	63	5.8	5.4
21	74	78	37	34	2.00	2.29	10.3	11.1	82	85	7.2	7.0
22	31	35	49	46	0.63	0.76	6.8	7.2	46	47	4.5	4.9
23	49	53	53	52	0.93	1.02	10.5	11.1	57	60	4.7	4.8
24	44	51	38	44	1.13	1.17	7.5	9.4	71	73	5.8	5.5
25	37	35	62	64	0.59	0.54	7.8	9.2	54	52	4.7	3.8
Control Patients (n = 12)												
Mean	48	49	54	56	0.97	0.96	9.4	10.6	59	60	5.2	4.7
±SD	±12	±12	±17	±17	0.33	±0.35	±1.6	±1.7	±10	±10	±1.1	±0.9
p value	NS		<0.05		NS		<0.0001		NS		<0.005	
Patients with Myocardial Infarction (n = 25)												
Mean	47	51	47	49	1.05	1.09	8.6	9.8	62	64	5.5	5.2
±SD	±15	±15	±10	±10	±0.40	±0.42	±2.2	±2.3	±10	±10	±1.2	±0.9
p value	<0.0001		<0.05		NS		<0.0001		<0.0001		<0.005	

Data are presented in the baseline (B) and postextrasystolic (PES) states in control subjects and patients with myocardial infarction.
B = baseline; E/A = the ratio of peak early filling wave velocity to peak atrial contraction wave velocity; E/TVI = peak early filling wave velocity normalized to time velocity integral during whole diastole; NS = not significant; Peak E, Peak A = peak velocities of early filling wave and atrial contraction wave; PES = postextrasystolic; TVI = time velocity integral during whole diastole; %TVI1 = percent increase of time velocity integral during the first half of diastole.

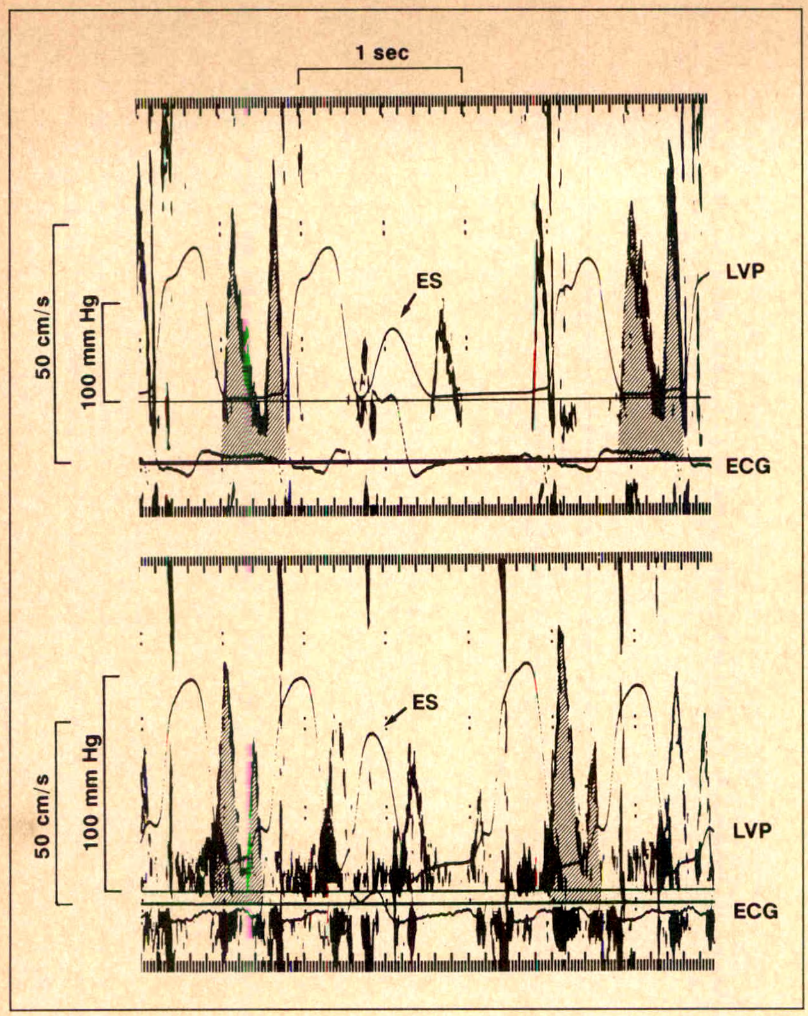

FIGURE 3. Pulsed Doppler echocardiography recorded simultaneously with left ventricular pressure (LVP) and electrocardiography (ECG) in a control group patient *(upper panel)* and in a patient with previous myocardial infarction *(lower panel).* Note that compared to the baseline beat, peak early velocity remained unaltered after the postextrasystolic beat in the control patient, whereas it increased in the patient with myocardial infarction. Time velocity integral during diastole, i.e., the area under the velocity curve, increased in both patients. ES = extrasystole.

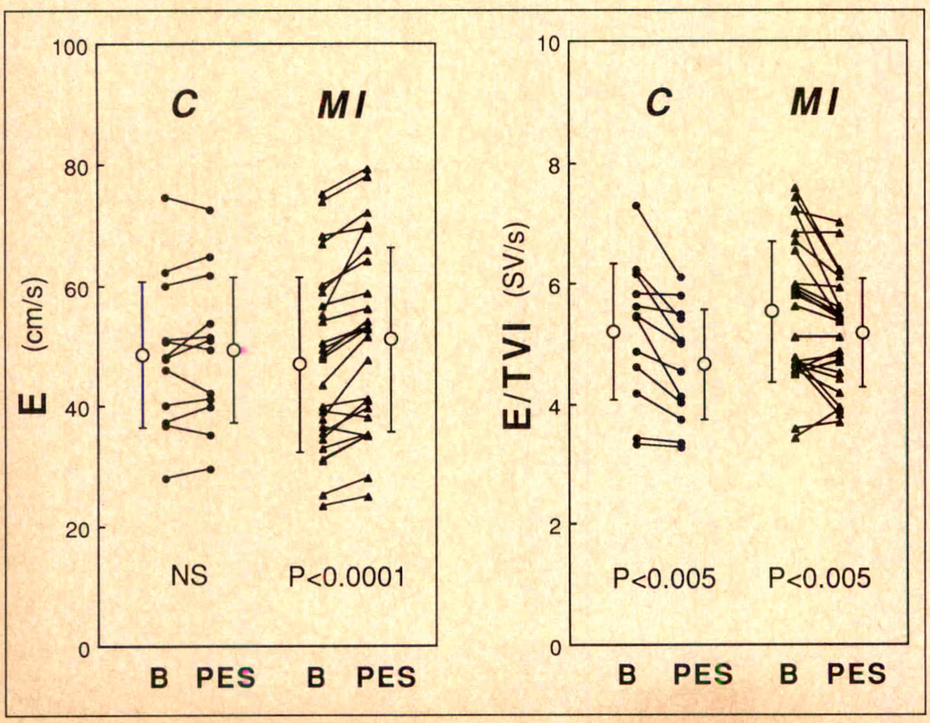

FIGURE 4. Individual data of Doppler echocardiographic peak early velocity (E) *(left panel)* and its normalization to time velocity integral (E/TVI) *(right panel)* during the baseline (B) beat and after postextrasystolic (PES) potentiation in the control group (C) and in patients with myocardial infarction (MI). *Open circle* and *bar* in each panel represent mean value ± 1 standard deviation, respectively.

the effects of PES contraction and relaxation on early diastolic filling in the clinical setting. Carroll et al[13] found cineangiocardiographically that early diastolic volumetric peak filling rate was not altered despite a prolonged relaxation after PES potentiation. Likewise, Stoddard et al[20] recently revealed, using pulsed Doppler echocardiography, that PES potentiation does not change early diastolic transmitral velocity profile in patients with coronary artery disease or those with aortic stenosis. In contrast, Paulus et al[14] reported that PES potentiation decelerated the rate of relaxation and worsened peak E-wave velocity in patients with hypertrophied left ventricle due to aortic stenosis or hypertrophic cardiomyopathy. Compared with these previous studies, PES enhancement of early diastolic filling in association with slowed left ventricular relaxation in our patients with MI is unique. In these patients, accompanying a greater augmentation of stroke volume, left ventricular minimum pressure decreased slightly in the PES beat. Since mitral valve opening pressure did not change, the atrioventricular pressure difference may increase, resulting in an accelerated peak E-wave velocity in our patients with MI.

Clinical implications: Recently, Doppler echocardiography allows noninvasive and serial measurement of early diastolic filling pattern easily. Among several Doppler parameters, peak E-wave velocity has been frequently used and is considered to be an index of diastolic function, i.e., left ventricular relaxation or compliance.[5,8,9] However, it is increasingly evident that impairment of early diastolic filling due to left ventricular relaxation or compliance abnormalities is mimicked and masked by the change in filling pressures.[2,4-6] It is possible to evaluate diastolic dysfunction indirectly from the assessment of early diastolic filling parameters in some clinical situations. The present study emphasizes that in this assessment of diastolic function, it is necessary to eliminate not only the potential effect of filling pressure, but also that of systolic ejection performance on early diastolic filling dynamics. Several investigators recently evaluated early diastolic filling profiles using volumetric peak filling rate normalized to stroke volume or total filling volume.[15,21-23] E/TVI is theoretically equal to this normalized filling rate. In this regard, although further study is needed for its pathophysiologic validity to be established, this normalized Doppler index may be useful in distinguishing between systolic and diastolic dysfunction.

Study limitations: Left ventricular diastolic peak filling rate is determined by the atrioventricular pressure gradient and the resistance to the flow at the time of its occurrence. In the present study, we did not assess direct effects of these factors on Doppler velocity indexes but assessed indirect ones of left ventricular contraction and relaxation, both of which contribute to the pressure gradient and resistance. However, it is not always possible to determine directly the pressure difference between the left atrium and ventricle or the resistance to the flow in the clinical setting. Ishida et al,[19] using electromagnetic flow probes in the canine heart, reported that the change in early diastolic peak filling rate could be explained to some extent by a combined function of both atrioventricular crossover pressure and the time constant of left ventricular pressure decline. Mitral valve opening pressure, a logical alternative to the crossover pressure, did not change significantly after PES potentiation in the control and MI groups. Analysis of the data suggests that PES enhancement of peak E wave and reduction of E/TVI in patients with MI is attributable to, respectively, an augmented systolic function, and slowed left ventricular pressure decline. In this study, the PES increase in angiographic %V1 was not significant, but the increase in Doppler %TVI1 was significant in patients with MI. Angiographic volumetric change provides 3-dimensional information, whereas Doppler echocardiographic velocity profile is essentially 1-dimensional. Although a relative Doppler index such as %TVI1 can minimize the dimensional problem, this methodologic difference might explain the discrepancies between angiographic and echocardiographic filling parameters.

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Relation of Serum Lipoprotein Cholesterol Levels to Presence and Severity of Angiographic Coronary Artery Disease

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To assess the relation of lipid levels to angiographic coronary artery disease (CAD), lipid profiles were obtained on 125 men and 72 women undergoing diagnostic coronary angiography. CAD, defined as ≥25% diameter narrowing in a major coronary artery, was present in 106 men (85%) and 54 women (75%). Multiple regression analyses revealed that only high-density lipoprotein (HDL) cholesterol level in men, and age and total/HDL cholesterol ratio in women, were independently associated with the presence of CAD after adjustment for other risk factors. HDL cholesterol level and age were significantly correlated with both extent (number of diseased vessels) and severity (percent maximum stenosis) of CAD in men. In women, age was the only independent variable related to severity, whereas age and total/HDL cholesterol ratio were related to extent.

Of 71 patients with total cholesterol <200 mg/dl, 79% had CAD. With multiple regression analyses, HDL cholesterol was the only variable independently related to the presence and severity of CAD in these patients after adjustment for age and gender; extent was significantly associated with age and male gender, and was unrelated to any of the lipid parameters.

With use of multiple logistic and linear regression analyses of the group of 197 patients, HDL cholesterol was the most powerful independent variable associated with the presence and severity of CAD after adjustment for age and gender. HDL cholesterol was also an independent predictor of extent. Age was independently associated with each of the end points examined, and was the variable most significantly related to extent. These data add to the growing body of information demonstrating an important association between HDL and CAD.

(Am J Cardiol 1991;67:479–483)

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A direct relation between levels of total and low-density lipoprotein (LDL) cholesterol and coronary artery disease (CAD) is well established.[1,2] Therapeutic reduction of elevated total and LDL cholesterol levels has been shown to decrease the risk for CAD.[3] Hence, the National Cholesterol Education Program recommends that a nonfasting total cholesterol level be determined in all adults for the purpose of identifying persons at high risk for CAD, who may benefit from intensive intervention efforts.[4] Routine determination of high-density lipoprotein (HDL) cholesterol level is not recommended. However, a strong and independent inverse relation between HDL cholesterol and CAD[5–8] has been established with few exceptions,[9,10] and there is mounting evidence that low levels of HDL cholesterol predict CAD even when total cholesterol levels are not elevated.[7,11,12]

Previous reports of angiographically defined CAD have shown a variety of independent correlates with lipid, lipoprotein and apolipoprotein levels.[13–19] The association of CAD and HDL cholesterol concentration has varied widely, ranging from significant inverse correlations to no correlation.[20,21]

This study reexamines the relation between angiographically defined CAD and lipid levels in patients undergoing elective diagnostic coronary angiography.

METHODS

Patient selection: The study group comprised 197 patients undergoing elective coronary angiography for evaluation of chest pain at Georgetown University Medical Center, who had adequate visualization of both the right and left coronary artery systems, and had a fasting lipid profile obtained the morning of the procedure. Patients with unstable angina, prior coronary artery bypass grafting, recent myocardial infarction (<8 weeks), and those taking lipid-lowering medications were excluded. Because these patients were preselected for coronary angiography, they do not represent a random sample of the general population.

Coronary arteriography: Selective coronary arteriograms were obtained using either the Judkins or Sones technique at the discretion of the individual angiographer. Filming was obtained using a 7-inch image intensifier and 35-mm film. Cine film was processed in the conventional manner and viewed on a Tagarno projector.

Coronary arteriograms were independently reviewed by 2 cardiac radiologists without prior knowledge of the

TABLE I Characteristics of Study Group		
	Men	Women
No. of patients	125	72
Age (years)	60 ± 1	64 ± 2*
Total cholesterol (mg/dl)	213 ± 4	226 ± 6
LDL cholesterol (mg/dl)	146 ± 3	149 ± 5
Triglycerides (mg/dl)	174 ± 10	154 ± 10
HDL cholesterol	40 ± 1	49 ± 2*
Total:HDL cholesterol	5.7 ± 0.2	5.4 ± 0.4
Coronary artery disease:		
Present (%)	85	75
Absent (%)	15	25
CAs narrowed ≥25% in diameter (no.)		
0	19	18
1	22	13
2	22	10
3	62	31
Severity (%)	71 ± 3	56 ± 5*

* $p < 0.05$ compared with those in men.
Values are mean ± standard error of the mean.
CA = coronary artery; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

lipid values. Each section of the arterial tree was viewed in multiple projections. Calipers were used to compare the diameter of a stenosed region with the nearest normal vessel diameter and stenoses were then classified as a percentage reduction of the original diameter.

CAD was considered present if ≥1 major coronary artery system (left anterior descending, circumflex, right coronary artery) had ≥25% diameter stenosis. When there was disagreement among the cardiac radiologists, the results were averaged. CAD was then classified by extent and severity. Extent was determined by the number of major coronary vessels containing at least 1 stenosis of ≥25% and was scored as number of vessels = 0, 1, 2 or 3. Severity was defined as the maximum percent stenosis found in any of the major coronary artery systems of a given patient.

Lipid and lipoprotein measurements: Total cholesterol[22] and triglyceride[23] levels were determined using enzymatic hydrolysis with formation of hydrogen peroxide and subsequent measurement spectrophotometrically using reagents from Boehringer Mannheim Diagnostics (Indianapolis, Indiana) and the Hitachi 737 (Tokyo, Japan) chemistry analyzer. Apolipoprotein B-containing lipoproteins were precipitated with magnesium chloride and phosphotungstic acid and subsequent centrifugation according to the manufacturer's specifications (Boehringer Mannheim Diagnostics).[24] Cholesterol measurement was then performed on the supernatant to determine HDL cholesterol concentration. LDL cholesterol was in turn calculated using a modified Friedewald formula[25,26]: LDL cholesterol = total cholesterol − (HDL cholesterol + triglyceride × 0.16).

Data analysis: Patients were grouped into those with and without CAD. Differences in mean age, lipid and lipoprotein values between the groups were evaluated using Student's *t* test. Stepwise multiple logistic regression analysis was used to assess the independent contribution of each of the variables on the occurrence of CAD among men and women, in those with total cholesterol <200 mg/dl, and in the entire study group.

Univariate Spearman correlation coefficients were computed for lipid values and age to characterize their relation to the extent and severity of CAD. Stepwise multiple linear regression analysis was used to evaluate the relative importance of several variables in contributing to the extent and severity of CAD. Differences were considered significant at $p < 0.05$.

RESULTS

Patient characteristics: The 197 patients comprising the study group were subdivided by gender: 125 men (63%) and 72 women (37%). Clinical data and lipoprotein profiles for men and women are listed in Table I. Mean age was higher in women than in men. No differences were observed between men and women with regard to mean levels of total cholesterol, LDL cholesterol or triglycerides, whereas HDL cholesterol was significantly higher among women. CAD tended to be present in a higher percentage of men than women, but this difference was not significant. The mean number of coronary arteries narrowed ≥25% in diameter was similar in men and women (2.0 ± 0.1 vs 1.7 ± 0.1), whereas women had significantly less severe maximum coronary artery stenoses.

Men: Data for men with and without CAD are listed in Table II. Mean age and mean levels of total and LDL cholesterol did not differ between men with and without CAD. There were significant differences in mean HDL cholesterol and triglyceride levels between

TABLE II Age, Plasma Lipids and Lipoproteins in Men and Women With and Without Coronary Artery Disease

	Men		Women	
	CAD Absent	CAD Present	CAD Absent	CAD Present
No. of patients (%)	19 (15)	106 (85)	18 (25)	54 (75)
Age (years)	57 ± 60	60 ± 1	56 ± 4	67 ± 2†
Total cholesterol (mg/dl)	215 ± 9	213 ± 4	217 ± 9	228 ± 7
LDL cholesterol (mg/dl)	145 ± 9	147 ± 4	140 ± 10	151 ± 6
Triglycerides (mg/dl)	137 ± 15	181 ± 11*	149 ± 22	155 ± 12
HDL cholesterol (mg/dl)	48 ± 3	39 ± 1†	53 ± 4	47 ± 2
Total:HDL cholesterol	4.8 ± 0.4	5.9 ± 0.2*	4.6 ± 0.4	5.6 ± 0.4*

* $p < 0.05$; † $p < 0.01$.
Values are mean ± standard error of the mean.
CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

men with and without CAD. Mean total/HDL cholesterol ratio was higher in the group with CAD.

With use of univariate analysis in men, the extent of CAD was significantly correlated with age ($r = 0.31$, $p < 0.001$) and low HDL cholesterol level ($r = -0.29$, $p < 0.001$). Similarly, severity of CAD was related to age ($r = 0.18$, $p < 0.05$) and low HDL cholesterol level ($r = -0.34$, $p < 0.0001$). Triglyceride level ($r = 0.18$, $p < 0.05$) and total/HDL cholesterol ratio ($r = 0.25$, $p < 0.01$) also were associated with severity, but not with extent. Levels of total and LDL cholesterol were unrelated to either extent or severity of CAD.

With stepwise multiple logistic regression analysis in men, using age and the various lipid and lipoprotein parameters as the independent variables, HDL cholesterol level was the lone variable associated with the presence of CAD ($p < 0.01$). Stepwise multiple linear regression analyses in men revealed that severity was most significantly related to low HDL cholesterol level ($p < 0.0001$) and secondarily related to age ($p < 0.05$), whereas extent correlated with age ($p < 0.001$) and low HDL cholesterol level ($p < 0.001$).

Women: Women with CAD were older and had a significantly higher mean total/HDL cholesterol ratio than those without CAD (Table II). Those with CAD tended to have a lower mean HDL cholesterol level, but this difference was not statistically significant. Mean levels of total cholesterol, triglycerides and LDL cholesterol did not differ among women with or without CAD.

Univariate analysis in women revealed that age was associated with both extent ($r = 0.36$, $p < 0.01$) and severity ($r = 0.39$, $p < 0.001$) of CAD. Extent also was related to low HDL cholesterol level ($r = -0.25$, $p < 0.05$) and total/HDL cholesterol ratio ($r = 0.27$, $p < 0.05$). HDL cholesterol level tended to be inversely related to severity of CAD ($r = -0.19$), but this relation was not statistically significant. None of the other lipid parameters was associated with severity of CAD in women.

Stepwise multiple logistic regression analysis in women revealed that age was the independent variable most strongly correlated with the presence of CAD ($p < 0.01$), and total/HDL cholesterol ratio was the only other variable selected ($p < 0.05$). Similarly, with stepwise multiple linear regression analyses in women, age ($p < 0.05$) and total/HDL cholesterol ratio ($p < 0.05$) were independently associated with extent, whereas age was the only variable correlated with severity ($p < 0.001$).

Patients with total cholesterol <200 mg/dl: Among the 197 patients comprising the study group, 71 (36%) had total cholesterol <200 mg/dl; CAD was present in 56 (79%) and absent in 15 (21%). When patients with were compared to those without CAD (Table III), there were no differences in mean levels of total cholesterol, LDL cholesterol or triglycerides. Those with CAD were significantlty older, had lower mean HDL cholesterol levels and higher mean total/HDL cholesterol ratio. Among the 71 patients, 20 (28%) had HDL cholesterol levels <35 mg/dl, and CAD was present in 18 (90%).

TABLE III Age, Plasma Lipids and Lipoproteins in Patients With and Without Coronary Artery Disease and Total Cholesterol <200 mg/dl

	CAD Absent	CAD Present
Number of pts.	15	56
Number of men/women	9/6	43/13
Age (years)	59 ± 3	65 ± 1*
Total cholesterol (mg/dl)	179 ± 4	173 ± 3
LDL cholesterol (mg/dl)	110 ± 5	113 ± 3
Triglycerides (mg/dl)	119 ± 14	147 ± 14
HDL cholesterol (mg/dl)	49 ± 4	39 ± 2†
Total:HDL cholesterol	4.0 ± 0.3	4.8 ± 0.2*

* $p < 0.05$; † $p < 0.01$.
Values are mean ± standard error of the mean.
CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

With use of univariate analysis in patients with total cholesterol <200 mg/dl, age correlated significantly with both extent ($r = 0.39$, $p < 0.001$) and severity ($r = 0.25$, $p < 0.05$) of CAD. There were significant inverse relations between HDL cholesterol level and both extent ($r = -0.36$, $p < 0.01$) and severity ($r = -0.42$, $p < 0.001$). Total/HDL cholesterol ratio also was associated with extent ($r = 0.30$, $p = 0.01$) and severity ($r = 0.35$, $p < 0.01$).

With use of age, gender, and the various lipid and lipoprotein parameters as independent variables, multiple logistic regression analysis revealed that the HDL cholesterol level was the only variable independently associated with the presence of CAD ($p = 0.01$) in patients with total cholesterol <200 mg/dl. Multiple linear regression analyses indicated that the HDL cholesterol level was the only variable independently associated with severity in patients with total cholesterol <200 mg/dl ($p < 0.001$), whereas extent was related to age ($p < 0.01$) and male gender ($p < 0.01$), and unrelated to any of the lipid parameters after adjustment for other risk factors.

Effects of beta blockers: Among patients with CAD, 29% of the men (n = 31) and 35% of the women (n = 19) were receiving β blockers. Mean HDL cholesterol levels were similar in CAD men and women with or without β-blocker use (37 ± 2 vs 40 ± 1 mg/dl in men; 45 ± 6 vs 47 ± 3 mg/dl in women). Similarly, mean levels of triglycerides, and total and LDL cholesterol did not differ in men or women with CAD who were receiving β blockers compared with those who were not.

Stepwise multiple regression analyses: A stepwise multiple logistic regression model was constructed using age, gender, and total, LDL and HDL cholesterol, triglycerides, and total/HDL cholesterol ratio as the independent variables to evaluate the effect of these factors on the occurrence of CAD in the entire study group of 197 patients. After adjustment for other risk factors, HDL cholesterol level was the most powerful independent variable related to the presence of CAD ($p < 0.001$), with age the only other variable selected ($p < 0.01$).

On stepwise multiple linear regression analyses using the same variables, HDL cholesterol level ($p < 0.0001$), age ($p < 0.001$) and male gender ($p < 0.05$) were independently associated with severity of CAD, whereas age ($p < 0.0001$) and HDL cholesterol level ($p < 0.0001$) were independently correlated with extent.

DISCUSSION

In this study we examined the relation between lipid levels and angiographically defined CAD in light of current guidelines for cholesterol screening, which do not recommend routine determination of HDL cholesterol in all patients.[4] The results indicate that of the lipid parameters examined, only the HDL cholesterol level was independently associated with the presence, severity and extent of CAD in the entire study group after adjustment for age and gender. Moreover, HDL cholesterol level was the strongest independent predictor of both the presence and severity of CAD. These findings are in accord with the results of previous studies[14,15,17,19,27] and conflict with others.[18,20,21] Neither total nor LDL cholesterol levels were related to any of the end points we examined. This contradicts the findings of many previous studies,[13,19-21] but corroborates those of others.[17] Similarly, triglyceride levels have previously been shown to correlate with pathologically[28] and angiographically[12,13,18,19,27] defined CAD, but were not an independent risk factor in our study.

Some gender differences were observed in our patients. In men, HDL cholesterol level was the best independent predictor of the presence and severity of CAD after adjustment for age. In women, age was the only factor associated with severity, and was the most powerful independent variable related to presence and extent. Of the lipid parameters, only total/HDL cholesterol ratio was an independent risk factor in women, correlating with both presence and extent of CAD after adjustment for age. Univariate analysis in women revealed that HDL cholesterol level was inversely and significantly related to extent, and there was a trend toward lower HDL cholesterol levels with increasing severity. However, after adjustment for other risk factors, HDL cholesterol level was not independently correlated with presence, severity or extent of CAD in women. Large epidemiologic studies have demonstrated the inverse relation of HDL cholesterol levels and CAD in women, particularly elderly women.[6,8] Thus, the disparity between men and women with respect to the inverse association of HDL cholesterol and CAD is likely related to the fewer number of women than men in our study, rather than to a biologic effect. Triglycerides have also been found to be an independent predictor of CAD in some studies, particularly among women.[18,19,29] However, triglyceride levels were unrelated to CAD among the women in our population.

Most CAD occurs in persons who have only mild or moderate elevations in cholesterol levels. Total cholesterol level alone is a poor predictor of CAD, particularly in older patients in whom the major lipid risk factor is the HDL cholesterol level.[6,7] A strong relation has been established between low levels of HDL cholesterol and the incidence of clinical CAD in subjects with total cholesterol <200 mg/dl.[6,7] Few data are available relating CAD as defined by angiography to lipid levels in patients with relatively low total cholesterol levels.[12] The HDL cholesterol level was the only variable independently related to the presence of CAD in our patients with total cholesterol <200 mg/dl after adjustment for age and gender. Similarly, HDL cholesterol was the only independent variable associated with severity in these patients, whereas extent was associated with age and male gender and was unrelated to any of the lipid variables. Thus, a low total cholesterol level, per se, does not necessarily signify a low risk of developing CAD. These findings underscore the importance of HDL cholesterol levels in predicting CAD among patients with total cholesterol levels that are considered normal, a group that comprises a large proportion (36% in this study) of patients undergoing coronary angiography.

The reasons for varying results among several studies correlating lipid levels to angiographically defined CAD are unclear but may relate to different patient populations. Moreover, it is difficult to compare results of various studies because of the differences in methods used in each study, particularly with respect to the definition of CAD used, and the wide assortment of techniques used to quantitate the severity of CAD. Since recent data have emerged suggesting that the angiographic severity of coronary stenoses does not predict the time or location of a subsequent coronary occlusion,[30] we chose to define the presence of CAD as ≥25% narrowing in a major coronary vessel in order to identify patients with early, but not necessarily clinically significant, atherosclerosis. The extent of CAD examines the number of diseased vessels, which has the advantage of separating patients with significant differences in prognosis, and the severity of CAD provides an additional measure of the clinical and hemodynamic significance of the atherosclerotic plaques.

Our data add to the growing body of information demonstrating an important association between HDL cholesterol levels and CAD.

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Edge Detection Versus Densitometry for Assessing Coronary Stenting Quantitatively

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The optimal method used to analyze quantitatively the immediate angiographic results of coronary stenting in the coronary arteries has not been studied. Accordingly, minimal luminal cross-sectional area was determined by 2 methods, edge detection and densitometry, in 19 patients who underwent percutaneous transluminal coronary angioplasty (PTCA) and then coronary stent implantation for symptomatic coronary stenoses. The correlation coefficient, 0.73 before angioplasty, decreased to 0.59 after coronary angioplasty and then increased to 0.83 after stent implantation. The mean differences between edge detection and densitometric determinations of minimal luminal cross-sectional area were 0.31 ± 0.51 mm^2 before PTCA, −0.38 ± 1.22 mm^2 after angioplasty and 0.35 ± 0.79 mm^2 after coronary stenting. It is concluded that, although the correlation and variability in the measurement of minimal luminal cross-sectional area between edge detection and densitometry deteriorate after PTCA, they are improved after stenting, probably because of smoothing of the vessel contours by the stent and remodeling of the stented segment into a more circular configuration. Therefore, in the stented coronary artery, edge detection and densitometry are equally acceptable methods of analysis.

(Am J Cardiol 1991:67:484–490)

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Stenting of the coronary arteries is currently being investigated as an adjunct to percutaneous transluminal coronary angioplasty (PTCA).[1] The optimal method used to analyze the immediate angiographic results of stenting in the coronary arteries has not yet been determined and is part of a general and unsettled controversy in the immediate assessment of PTCA. Computer-based automatic edge detection angiographic analysis systems have reduced the variability resulting from visual and caliper-determined contour detection,[2–4] but their use may be limited in eccentric lesions, particularly after angioplasty, when acute tears and dissections additionally distort the anatomy. Densitometry has been proposed as an alternative method of angiographic assessment of the severity of coronary obstructions because it is independent of the geometric shape.[5,6]

The hemodynamic significance of a lesion has previously been shown to be most closely correlated with the minimal cross-sectional area.[7,8] The determination of this parameter from edge detection programs from a single projection requires an assumption, often incorrect, that the vessel cross section is circular.[9,10] Our group has previously shown that discrepancies exist in the postangioplasty analysis between edge detection and videodensitometric methods, although conflicting data have also been published.[5,11,12] However, the situation after stenting of the coronary arteries may be altered, because the arterial wall typically assumes a smoother, more circular appearance. We therefore undertook this study to determine if stenting of coronary arteries after PTCA improves the correlation and agreement between videodensitometry and edge detection methods.

METHODS

Study patients: Nineteen patients, 13 men and 6 women, ranging in age from 41 to 70 years (mean 56), were enrolled after giving informed consent for stent implantation. The dilated and stented coronary artery was the left anterior descending coronary artery in 12 patients, the circumflex coronary artery in 2, the right coronary artery in 3 and a coronary artery bypass vein graft in 2. This series consisted of the first 19 patients in whom edge detection and videodensitometry were used to evaluate the immediate results of the procedure. In each patient, the coronary artery stenosis was dilated first. After successful angioplasty, the balloon catheter was exchanged for the stent delivery system over a 0.014-inch exchange guidewire. Unconstrained stents of 15 or 20 mm in length, depending on the lesion, were

TABLE I Quantitative Angiographic Data

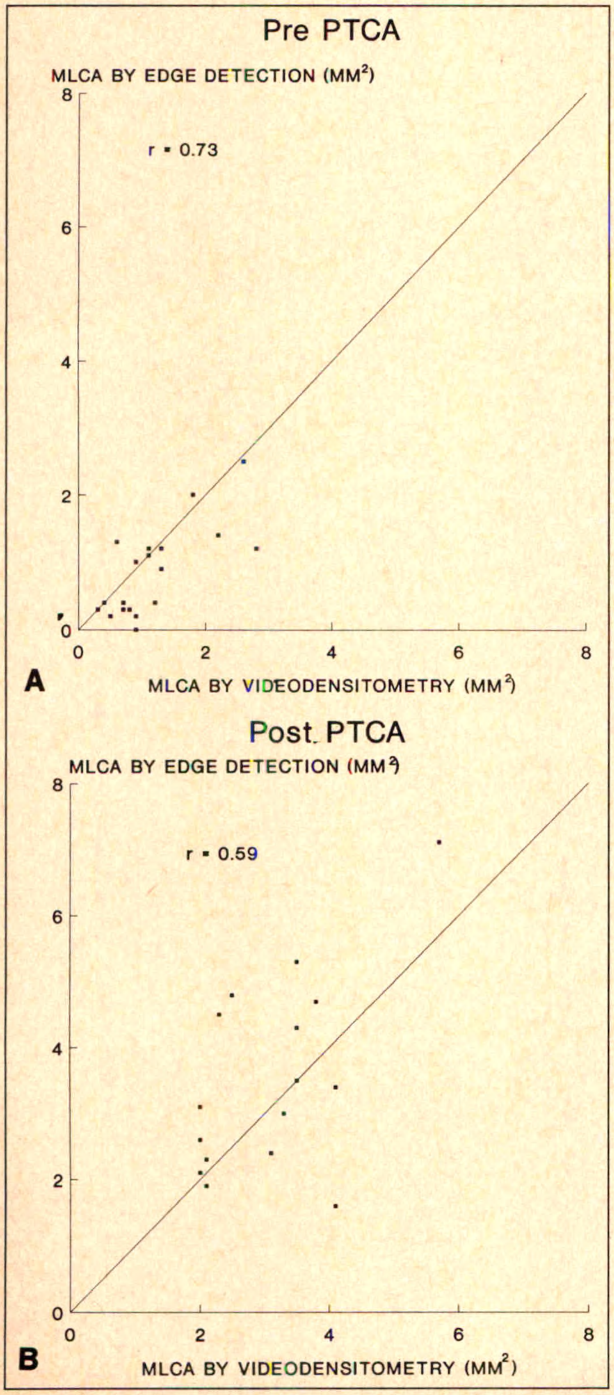
Pt. No.	Age (yr) & Sex	PTCA Vessel	Obstruction Diameter (mm)	Diameter Stenosis (%)	Minimal Luminal Cross-Sectional Area: Edge Detection (mm^2)	Minimal Luminal Cross-Sectional Area: Densitometry (mm^2)
1 PreP	70M	Conduit	0.9	67	0.7	0.4
PostP			2.2	24	3.8	4.7
PostS			3.0	8	7.1	7.1
2 PreP	70M	Conduit	1.2	55	1.2	0.4
PostP			1.6	22	2.1	2.3
PostS			2.3	10	4.1	2.3
3 PreP	52M	Right	1.8	50	2.6	2.5
PostP			2.1	46	3.5	5.3
PostS			2.8	23	6.1	5.7
4 PreP	42M	LAD	1.0	54	0.9	0.2
PostP			1.6	31	2.1	1.9
PostS			1.8	23	2.5	2.7
5 PreP	52M	LAD	1.3	47	1.3	0.9
PostP			—	—	—	—
PostS			1.7	26	2.3	1.1
6 PreP	46M	Right	1.0	67	0.7	0.3
PostP			1.8	46	2.5	4.8
PostS			2.5	28	4.9	5.7
7 PreP	69M	LAD	1.1	62	0.9	1.0
PostP			1.6	40	2.0	2.1
PostS			2.1	28	3.5	3.0
8 PreP	64F	LAD	1.5	48	1.8	2.0
PostP			2.0	26	3.3	3.0
PostS			2.2	21	3.8	3.6
9 PreP	62F	LAD	0.7	73	0.4	0.4
PostP			—	—	—	—
PostS			2.2	16	3.8	4.0
10 PreP	51M	LAD	1.7	27	2.2	1.4
PostP			2.0	21	3.1	2.4
PostS			2.3	15	4.1	3.6
11 PreP	41M	LAD	0.6	81	0.3	0.3
PostP			1.6	51	2.0	2.6
PostS			2.5	30	4.9	3.8
12 PreP	51F	LAD	0.9	61	0.6	1.3
PostP			2.1	25	3.5	4.3
PostS			2.0	26	3.1	2.9
13 PreP	69M	LAD	1.3	59	1.3	1.2
PostP			2.1	30	3.5	3.5
PostS			2.4	20	4.5	4.5
14 PreP	51F	Right	1.0	60	0.8	0.3
PostP			2.3	22	4.1	3.4
PostS			2.4	21	4.5	5.0
15 PreP	54M	LC	1.2	52	1.1	1.1
PostP			1.6	39	2.0	2.6
PostS			2.3	26	4.1	4.1
16 PreP	55F	LC	0.8	61	0.5	0.2
PostP			1.6	37	2.0	3.1
PostS			1.9	25	2.8	2.6
17 PreP	54F	LAD	1.2	61	1.1	1.2
PostP			1.7	35	2.3	4.5
PostS			2.1	20	3.5	3.9
18 PreP	52M	LAD	1.9	52	2.8	1.2
PostP			2.7	39	5.7	7.1
PostS			1.9	36	2.8	2.5
19 PreP	65M	LAD	1.1	63	0.9	0.0
PostP			2.3	17	4.1	1.6
PostS			2.6	13	5.3	2.9
Mean ± SD						
PreP			* 1.2 ± 0.4	* 58 ± 11	1.2 ± 0.7	0.9 ± 0.7
PostP			1.9 ± 0.3	32 ± 10	3.0 ± 1.0	3.5 ± 1.5
PostS			† 2.3 ± 0.3	* 22 ± 7	4.1 ± 1.2	3.9 ± 1.4

* P = 0.0000; † p = 0.0002.
LAD = left anterior descending artery; LC = left circumflex artery; PreP = before percutaneous transluminal coronary angioplasty; PostP = after percutaneous transluminal coronary angioplasty; PostS = after stenting; Right = right coronary artery; SD = standard deviation.

placed to cover the entire dilated arterial segment. Medications at the time of the initial angiogram were intravenous heparin, acetylsalicylic acid, dipyridamole, nitrates and calcium antagonists. Coronary angiograms were performed before and after angioplasty, and after stent implantation.

Description of the stent: In this trial, the endovascular prosthesis, Wallstent®, was provided by Medinvent SA, Lausanne. The method of implantation and description of this stent have been reported previously.[13,14] This stent is a self-expandable, stainless steel-woven mesh prosthesis that can be positioned in the coronary artery with the standard over-the-wire technique through an 8Fr or 9Fr guiding catheter. The device is constructed of sixteen 0.08-mm-wide wire filaments. It is constrained in an elongated configuration on a 1.57-mm-diameter delivery catheter, with the distal end covered by a removable plastic sleeve. As the sleeve is withdrawn, the constrained device returns to its original unconstrained larger diameter and becomes anchored against the vessel wall. Unconstrained stent diameter was selected to be 0.50 mm larger than the reference diameter of the stented vessel.

Quantitative coronary angiography: All cineangiograms were analyzed with the computer-assisted cardiovascular angiography analysis system, which has been discussed in detail previously.[15–18] The important steps will be briefly described. Any area sized 6.9 × 6.9 mm in a selected cineframe (overall dimensions 18 × 24 mm) encompassing the desired arterial segment can be digitized by a high-resolution CCD-camera with a resolution of 512 × 512 pixels and 8 bits of gray level. Vessel contours are determined automatically based on the weighted sum of the first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions of an arterial segment. A computer-derived estimation of the original arterial dimension at the site of the obstruction is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease



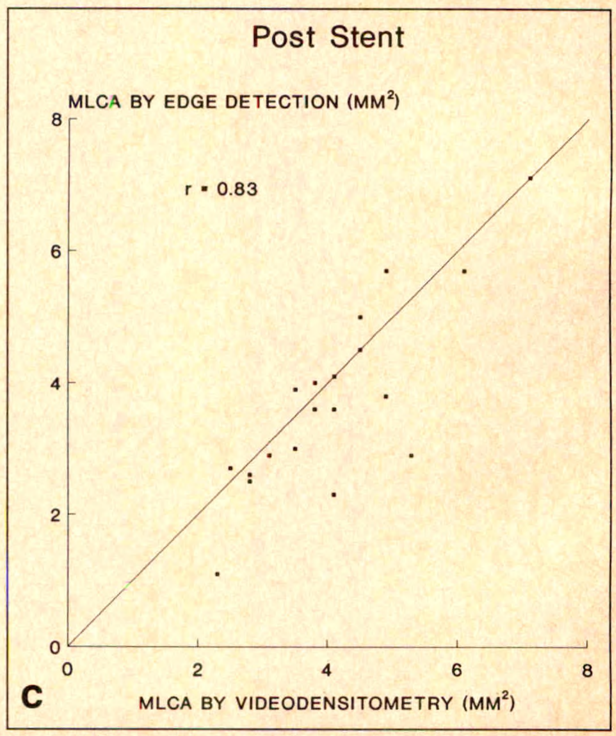


FIGURE 1. Individual data for minimal luminal cross-sectional area (MLCA) determined by edge detection and videodensitometry *(A)* before and *(B)* after percutaneous transluminal coronary angioplasty (PTCA) and *(C)* after stenting. *Diagonal line*, equal measurements by the 2 methods. Values above line were higher by edge detection and below line higher by densitometry.

present) according to the diameter function. The absolute diameter of the stenosis as well as the reference diameter are measured by the computer, which uses the known guiding catheter diameter as a calibration factor. All contour positions of the catheter and arterial segments are corrected for pincushion distortion. The minimal cross-sectional area of the narrowed segment and the interpolated percent area stenosis are then derived by assuming a circular model and comparing the observed stenosis dimensions to the reference values. The angiographic analysis was done using the view in which the arterial narrowing appeared the most severe and all interventions were performed.

Densitometric analysis: Densitometry is based on the approximate linear relation that exists between the optical density of a contrast-enhanced lumen and the absolute dimensions of the arterial segment. Constitution of the relation between the path length of the x-rays through the artery and the brightness values requires a detailed analysis of the complete x-ray/cine/video chain, including the film development process.

For the first part of the chain, from the x-ray tube to the output of the image intensifier, we use Lambert Beer's law for the x-ray absorption and apply certain models for the x-ray source and the image intensifier. From the output of the image intensifier up to the brightness values in the digital image, we use a simple linear transfer function. Details of this technique have been described elsewhere.[5,15-18]

The cross-sectional area of a vessel is then obtained as follows: When selecting a cineframe for the densitometric analysis, we ensure that the main axis of the segment is reasonably perpendicular to the incoming x-rays (i.e., a nonforeshortening view is chosen). Contours of the artery are detected by automated contour detection as previously described. From the measured diameters along the analyzed segment, the diameter data described above are derived. On each scanline perpendicular to the local centerline direction of the vessel, a profile of brightness values is measured. This profile is transformed into an absorption profile by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly left and right of the detected contours. Subtraction of this background portion from the absorption profile within the arterial contours yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-sectional area at the particular scanline. By repeating this procedure for all scanlines, the cross-sectional area function is obtained. A reference densitometric area is obtained following the same principles as previously described for the diameter measurements. It is clear that homogeneous mixing of the contrast agent and the blood must be assumed for the measurement to be correct. The complete procedure has been evaluated with the cinefilms of Plexiglas® models of coronary obstructions.[16]

To determine whether the physical properties of the stent itself interfere with the densitometric assessment, Wallstents® were placed inside known stenoses within perspex models and the minimal luminal cross-sectional area was calculated by densitometry. These cylindrical models, 5 mm in diameter at the ends and tapering to either 2 or 3 mm in the center, were filled with iopamidol (50 or 100% concentration) and angiographic studies were done at 75 kV to approximate the clinical setting. The calculated values for minimal luminal cross-sectional area were 0 to 12% higher in the stented models, compared with identical phantoms that did not contain stents.

Statistical analysis: The individual data for minimal luminal diameter and minimal luminal cross-sectional area by edge detection and densitometry, respectively, were used to calculate the mean value ± standard deviation (Table I). Analysis of variance was performed to compare the mean minimal luminal diameter before and after PTCA and after stenting and, if significant differences were found, 2-tailed *t* tests were applied. A value <0.05 was considered statistically significant.

To measure the strength of the relation between the 2 methods of analysis—edge detection and densitometry—in determining minimal luminal cross-sectional area, the product-moment correlation coefficient (r) and its 95% confidence intervals were calculated at the 3 distinct times of study. The agreement between the 2 measures was assessed by determining the mean and the standard deviation of the between-method difference, as

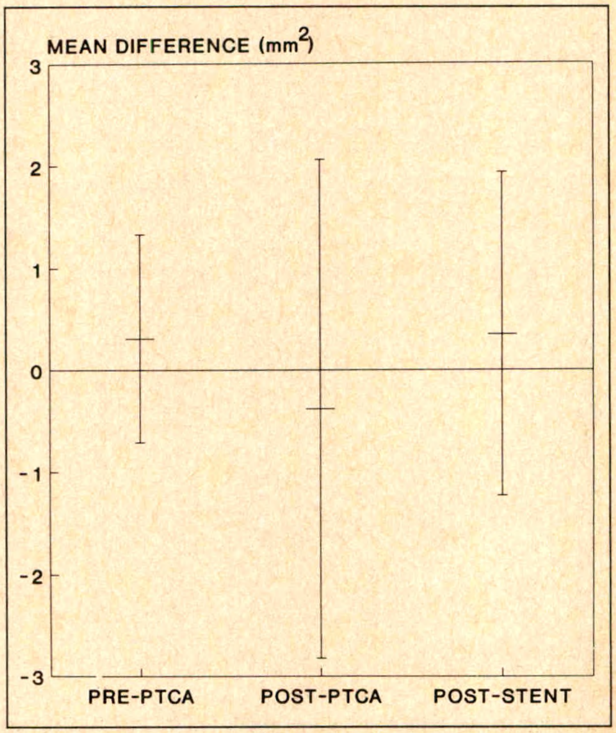


FIGURE 2. Mean difference between edge detection and densitometry and 95% confidence intervals before and after percutaneous transluminal coronary angioplasty (PTCA) and after stenting. Mean differences were slightly positive (0.31, 0.35 mm²) before PTCA and after stenting, respectively, and slightly negative (−0.38 mm²) after PTCA. The widest 95% confidence interval was in the analysis after PTCA, indicating the poorest association between the 2 methods, compared with the analysis before PTCA and after stenting.

suggested by Bland and Altman.[19] At each interval this was done by computing the sum of the individual differences between the 2 methods to determine the mean difference and the standard deviation.

RESULTS

The individual data obtained by contour detection and videodensitometric analysis are listed in Table I. There was an overall significant increase in the minimal luminal diameter and a decrease in percent diameter stenosis after angioplasty (1.2 ± 0.3 to 1.9 ± 0.3 mm and 58 ± 11 to 32 ± 10%, respectively) and after stenting (2.3 ± 0.3 mm, 22 ± 7%).

The correlation between edge detection and densitometry in the assessment of minimal luminal cross-sectional area before and after PTCA, and after stenting is shown in Figures 1A, 1B and 1C, respectively. Before angioplasty, correlation coefficient was 0.73 (95% confidence interval, 0.41 to 0.89), indicating a reasonably linear relation. However, this deteriorated after PTCA, resulting in a correlation coefficient of 0.59 (95% confidence interval, 0.15 to 0.83). However, linearity was significantly improved with the implantation of a coronary stent (correlation coefficient, 0.83; 95% confidence interval, 0.61 to 0.93).

The agreement between the 2 measures is illustrated in Figure 2. The determination of minimal luminal cross-sectional area was slightly higher by edge detection than by videodensitometry in the before PTCA and after stenting analyses (mean differences, 0.31 and 0.35 mm^2, respectively) and slightly lower after PTCA (mean difference, -0.38 mm^2). The variability as deter-

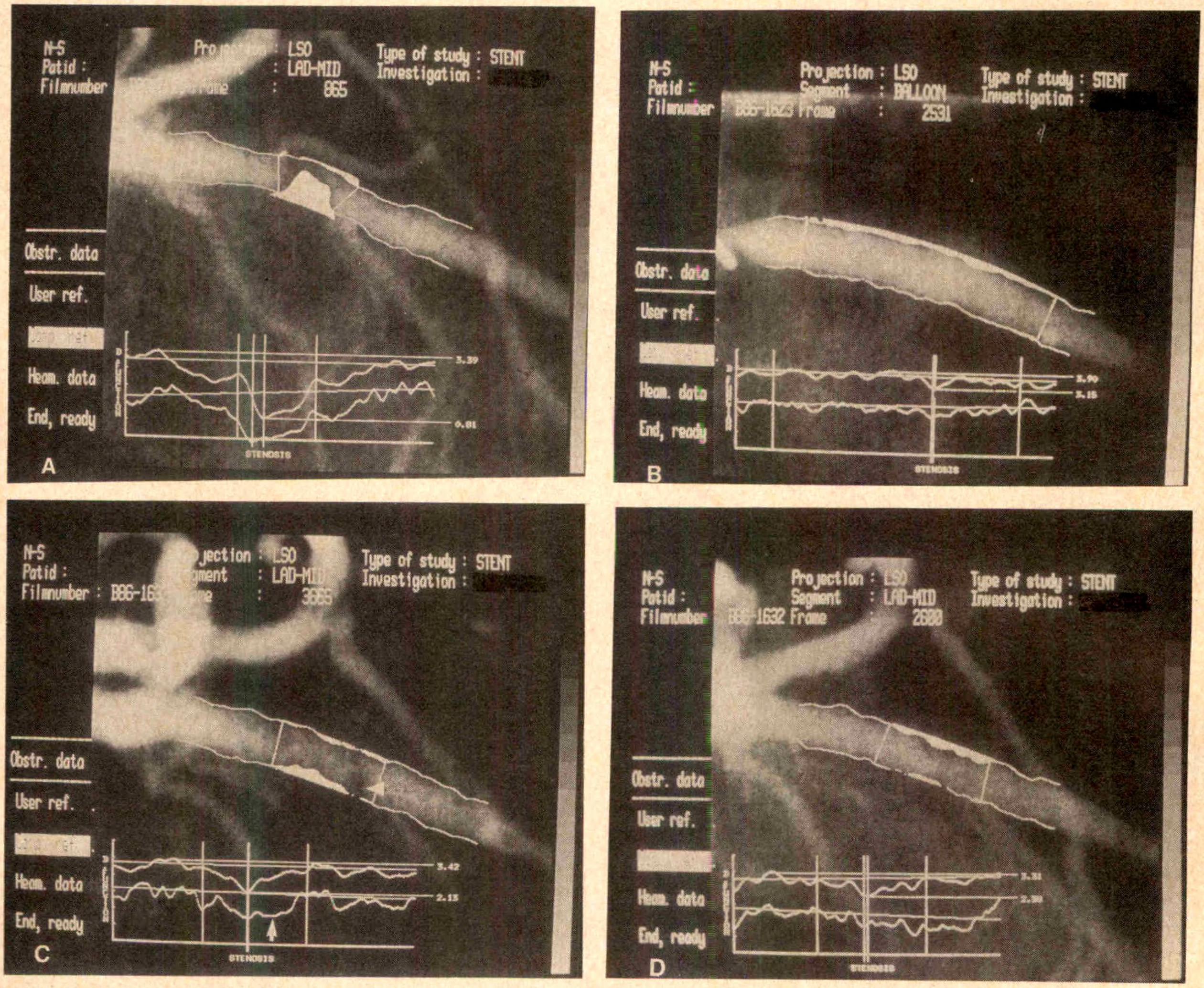


FIGURE 3. Edge contour and densitometric analysis of an obstruction in the left anterior descending (LAD) artery before percutaneous transluminal coronary angioplasty [PTCA] *(A)*, during balloon inflation *(B)*, after PTCA *(C)* and after stenting *(D)*. Graphs show the diagnostic diameter function *(upper curve)* and the densitometric area function *(lower curve)*. *Lower horizontal line* (0.81 mm in frame A) is the minimal luminal diameter. *Outside vertical lines* on the graph and the 2 *vertical lines* on the angiogram are lesion boundaries. *Inner vertical lines* on graph are the site in the lesion of minimal luminal diameter. In the angiogram before PTCA *(A)*, contour and densitometry curves are parallel. There was a marked improvement in the minimal luminal diameter of the lesion during balloon inflation *(B)*. After PTCA *(C)*, contour and densitometry curves diverge *(arrow)* at the site of an intraluminal haziness *(arrowhead)*. In the diameter function, there is a descending limb of the curve that reaches a nadir and immediately is followed by an ascending limb. However, the densitometry curve shows a descending limb followed by a plateau. After stenting *(D)*, the relation between the 2 curves is restored.

mined by the standard deviation of the differences between the 2 measurements was highest in the analysis after PTCA (1.22 mm^2), compared to before PTCA and after stenting (0.51 and 0.79 mm^2, respectively). An individual example is shown in Figure 3.

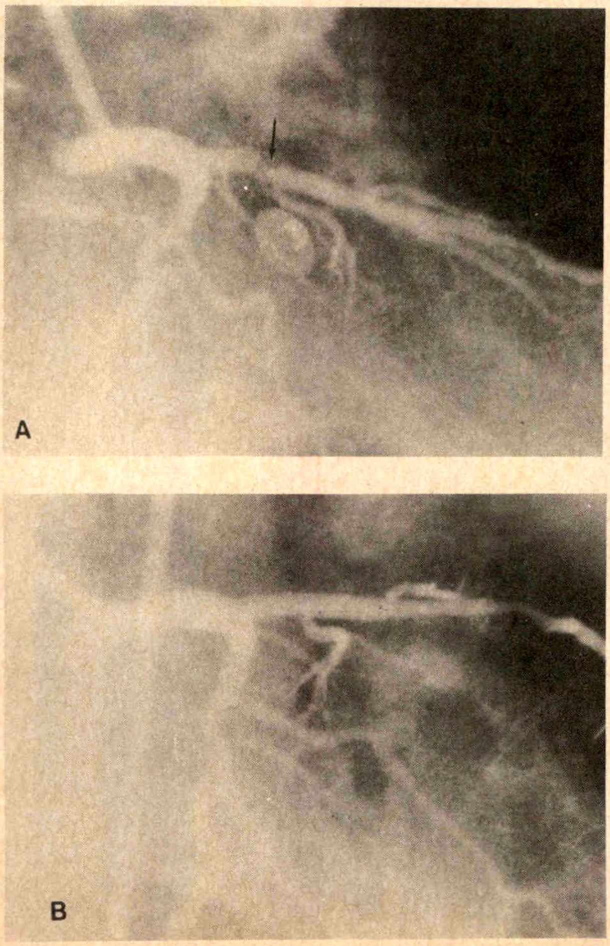
DISCUSSION

The ideal method by which to perform angiographic analysis after coronary interventions, including balloon angioplasty and stenting, remains debatable. Although densitometry is independent of geometric shape, its application is limited in the presence of branch vessels that may cause errors in the background correction technique and in situations where the x-ray beam is not perpendicular to the long axis of the vessel. Additional clinical factors that contribute to the inaccuracy of densitometry include x-ray scatter, light scatter within the image intensifier (veiling glare) and beam hardening of the polychromatic x-ray flux because of iodine and tissue thickness. Discrepancies between edge detection and densitometry are most likely to occur when the shape of the vessel wall at the level of the lesion deviates furthest from a circular configuration, because this is a basic assumption in the calculation of minimal luminal cross-sectional area by edge detection.

This study illustrates several important points. First, we have shown that a relation exists between the 2 measurements at all stages of the procedure, but the strength of this relation, based on the magnitude of the correlation coefficient, deteriorates after PTCA and then improves after stenting. Furthermore, although mean differences between the 2 methods were small in all analyses, the greatest variability and thus the poorest agreement occurred in the analysis after PTCA. The before and after PTCA results are in accordance with earlier observations by our group.[5] At that time we suggested that measurement of cross-sectional area from a single view is inaccurate. Subsequent studies by Tobis et al[11] comparing edge detection in 2 orthogonal views and by Lesperance et al[12] comparing single versus the mean of multiple views have shown similar and high correlations both before and after PTCA. However, use of the correlation coefficient alone is not an adequate measure of agreement between 2 measurement techniques for several statistical reasons.[19,20] Determination of the mean and standard deviation of the between-method differences should be included in the analysis.

Two factors probably contributed to the improved agreement after stent implantation. Vessel contours appeared more regular and smooth and in some cases intimal flaps appeared to be tacked back by the scaffolding property of this stent. However, even more important, the self-expanding property of this stent not only additionally dilated the vessel, but also probably remodeled the stented segment into a more circular geometry. This has previously been shown in vivo after the implantation of coronary stents in animals and in some human coronary vessels (Figure 4, A, B and C).

A potential limitation of densitometry in the analysis after stenting may be a spuriously high determination of minimal luminal cross-sectional area (up to 12% in the



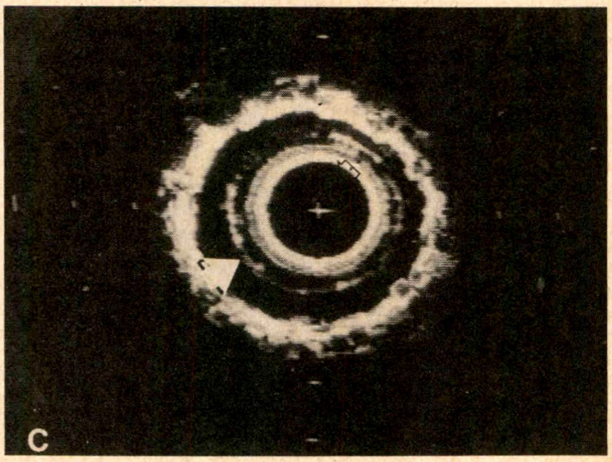


FIGURE 4. *A*, angiogram of left anterior descending artery stenosis after dissection *(arrow)* during percutaneous transluminal coronary angioplasty. *B*, angiographic appearance of left anterior descending artery lesion after stenting showing smooth contour. *C*, in vitro intravascular ultrasound examination of this vessel 24 hours after stenting (patient died from intracerebral hemorrhage 12 hours after stenting). The inner circle is due to intravascular probe. The outer echodense pattern is due to stent wires *(large arrow)*. The lumen *(small open arrow)* is the echo-free space inside the stent. The stent effectively tacked back the dissection and restored the circular configuration of the vessel (courtesy of Dr. Bernardino Tucillo).

phantom studies) because of interference from the stent itself. This is probably related to the composition of the stent, surface area or additional factors, such as increased scatter in the stenotic section because of the stent. Although the mean differences in minimal luminal cross-sectional area between the edge detection and densitometry were small, the negative mean difference in the analysis after stenting (i.e., larger values by densitometry) in contrast to the positive mean difference after PTCA can be partly explained by this contribution of the stent to the densitometrically determined values. The effect of other currently available stents should be separately assessed and considered in angiographic analyses using densitometry.

Acknowledgment: We gratefully acknowledge the statistical assistance of Jan Tijssen, PhD.

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Frequency of Success and Complications of Coronary Angioplasty of a Stenosis at the Ostium of a Branch Vessel

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The authors of this study hypothesized that percutaneous transluminal coronary angioplasty of a stenosis at the ostium of a branch vessel, whether isolated or associated with a bifurcation stenosis, was associated with reduced procedural success and increased in-hospital complications. One hundred six patients with 119 ostial branch stenoses were compared with 1,168 patients who underwent angioplasty of nonostial branch stenoses. An ostial branch stenosis was defined as a stenosis in the proximal 3 mm of a major branch vessel (diagonal [n = 58], posterior descending [n = 21], obtuse marginal [n = 34] and intermediate [n = 6]). The ostial branch stenosis was isolated in 61% of the patients and associated with a bifurcation stenosis in 39%. Despite a balloon to artery ratio of 1.05:1, angiographic success was 74% of ostial branch stenoses versus 91% of nonostial stenoses (p <0.01). Furthermore, angioplasty of ostial branch stenoses resulted in a complication rate of 13 versus 5% for angioplasty of nonostial branch stenoses (p <0.01). Therefore, angioplasty of ostial branch stenoses results in decreased procedural success and significant residual stenosis despite adequate balloon sizing, suggesting arterial elastic recoil and a significant increase in complications.

(Am J Cardiol 1991;67:491–495)

From the Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, Minnesota. Manuscript received August 8, 1990; revised manuscript received October 25, 1990, and accepted October 26.

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Percutaneous angioplasty for ostial lesions in the right coronary artery,[1] the left anterior descending[2] and renal arteries[3] have been associated with low technical success rates and increased complications. We have found that coronary angioplasty for a stenosis at the ostium of a branch coronary artery can also present technical difficulties. We therefore reviewed our experience in this subgroup of patients and sought to determine if angioplasty of a stenosis at the ostium of a branch coronary artery, regardless of whether it represented an isolated ostial branch stenosis or a bifurcation stenosis, was associated with increased procedural risks, poorer overall results, and more frequent in-hospital complications. Furthermore, although double-wire and double-balloon techniques used for bifurcation stenoses have been shown to preserve side branch patency,[4–9] there is little information as to their effect on successful dilation or prevention of angioplasty-related complications attributable to dilation of the ostial branch vessel.

METHODS

Patients: Between November 1987 and January 1989, 1,274 patients underwent percutaneous transluminal coronary angioplasty (PTCA) at the Minneapolis Heart Institute, Abbott Northwestern Hospital. Of these 1,274 patients, 106 patients with 119 stenoses involving the ostium of a branch coronary vessel were retrospectively identified. All patients demonstrated a >50% reduction in percent diameter within 3 mm of the bifurcation of a large epicardial coronary artery. Isolated ostial branch stenoses (n = 65 patients) and bifurcation stenoses (n = 41 patients) were included for analysis.

Procedure: Angioplasty was performed using standard techniques in all patients. All patients were premedicated with aspirin and a calcium antagonist. Angioplasty was performed after ≥10,000 units of intravenous heparin were administered to obtain an activated clotting time of >300 seconds. The femoral approach was used in nearly all patients. Identical angiographic views, used for quantitative measurements, were obtained before and after PTCA, after the routine administration of 100 to 200 μg of intracoronary nitroglycerin. The following coronary angioplasty techniques were used depending on the coronary anatomy present: (1) single-balloon and wire technique (n = 65), and (2) double-balloon technique (n = 41), with successive or simultaneous inflations.

TABLE I Demographic and Clinical Data	Ostial Branch Stenosis (n = 106)	Nonostial Branch Stenosis* (n = 1,168)
Age (mean)	62 ± 10.7	61 ± 10.2
Men/women (%)	75 (71)/31 (29)	864 (74)/304 (26)
Clinical presentation		
Stable angina (%)	36 (34)	467 (40)
Unstable angina (%)	49 (46)	444 (38)
Recent AMI (%)	16 (15)	327 (28)
Class III or IV angina	82 (77)	1,016 (87)
Risk factors for CAD		
Cigarette smoking (%)	69 (65)	747 (64)
Systemic hypertension >150 mm Hg systolic (%)	55 (52)	572 (49)
Diabetes mellitus (%)	12 (11)	117 (10)
Serum total cholesterol >200 mg/dl	50 (47)	455 (39)
Family history (%)	40 (38)	514 (44)
Previous CABG (%)	11 (10)	117 (10)
Prior AMI (%)	45 (42)	537 (46)

* p = difference not significant for all variables.
AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; CAD = coronary artery disease.

Data acquisition and analysis: Demographic, clinical, angiographic and follow-up data were obtained in all patients undergoing coronary angioplasty and were included in a computerized coronary angioplasty data base.

Angiographic data obtained included the location of all significant coronary artery stenoses, quantitative measurements using a Hewlett-Packard electronic caliper in ≥2 identical orthogonal views (percent diameter stenosis and balloon to artery ratio), lesion morphology, and the presence or absence of localized or propagating intimal dissection. An angiographically successful coronary angioplasty was defined by residual diameter stenosis <50%. In this study, if multivessel or bifurcation angioplasty was performed, success was determined by assessing residual stenosis in the ostial segment.

The following in-hospital complications were analyzed: abrupt closure, emergent coronary bypass, recurrent angina, delayed closure, periprocedural myocardial infarction, delayed coronary bypass, repeat in-hospital PTCA and death. Clinical success was defined as angiographic success plus none of the above-mentioned major complications occurring during the hospitalization. In patients with multivessel coronary angioplasty or bifurcation lesions, complications were included in the analysis if they were clearly related to the angioplasty of the ostial branch stenosis. The data obtained from patients who underwent coronary angioplasty of a stenosis at the ostium of a branch vessel were compared with our general cohort of patients who underwent angioplasty of a lesion (or lesions) not localized at the ostium of a coronary side branch.

Statistics: Continuous variables are expressed as mean ± standard deviation. Chi-square analysis or Fisher exact tests were used to compare categorical variables. Differences were accepted as significant if the p value was <0.05. Analyses were performed on an IBM computer using SAS statistical packages.

RESULTS

The clinical, demographic and procedure data for the ostial and nonostial branch stenosis groups are listed in Tables I and II. Despite a mean of 4 fully inflated balloon dilations at 8 atm for 100 seconds each (balloon to artery ratio of 1.05:1), angiographic angioplasty success was obtained in 74% of the ostial versus 91% of the nonostial branch stenosis groups ($p < 0.01$). Furthermore, the complication rate (abrupt closure, emergency coronary artery bypass surgery, myocardial infarction or death—Table III) was 13% with angioplasty of ostial branch stenoses versus 5% for PTCA of nonostial branch stenoses ($p < 0.01$).

For patients with bifurcation ostial branch stenosis, a double-balloon technique was performed if the primary vessel had an associated significant stenosis at the bifurcation. The outcome for the branch vessel was not affected by the specific angioplasty technique performed. Successful dilation of the ostial branch stenosis was obtained in 74% of the patients when a single-wire and balloon technique was used versus 78% when a double-balloon technique was used (difference not signifi-

TABLE II Percutaneous Transluminal Coronary Angioplasty: Procedure Data

	Ostial Branch Stenosis (n = 119)	Nonostial Branch Stenosis (n = 1,553)
Technical PTCA success	88 (74%)*	1,413 (91%)*
% diameter stenosis		
Before PTCA	74%	72%
After PTCA	35%	28%
Number of dilations (mean)	4	4
Atmospheres (mean)	8	9
Duration (mean)	100 seconds	134 seconds
Balloon:artery ratio	1.05:1	1.08:1
Diagonal	58 (49%)	
Posterior descending	21 (18%)	
Obtuse marginal	34 (29%)	
Intermediate	6 (4%)	

* p <0.01.
PTCA = percutaneous transluminal coronary angioplasty.

cant). The residual ostial stenosis in the bifurcation cases was persistent throughout the procedure and did not appear to be the result of "snow plowing" from dilation of the primary vessel. In addition, there was no difference in in-hospital complications when a double-balloon technique was used (6.3 vs 6.6%). The success rate for the primary vessel in these bifurcation cases was 91%. Complications in the primary vessel were 3%.

Representative cases of coronary angioplasty of both isolated ostial branch stenoses and ostial branch steno-

TABLE III In-Hospital Complications

	Ostial Branch Stenosis (n = 106)	Nonostial Branch Stenosis (n = 1,168)
Abrupt closure (%)	10 (9)	47 (4)
Emergent CABG (%)	4 (4)	25 (2)
AMI (%)	2 (1.8)	15 (1)
Death (%)	0 (0)	2 (0.2)
Complications (abrupt closure, AMI, emergency CABG or death) (%)	14 (13)*	58 (5)

* p <0.01.
CABG = coronary artery bypass graft surgery; AMI = acute myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

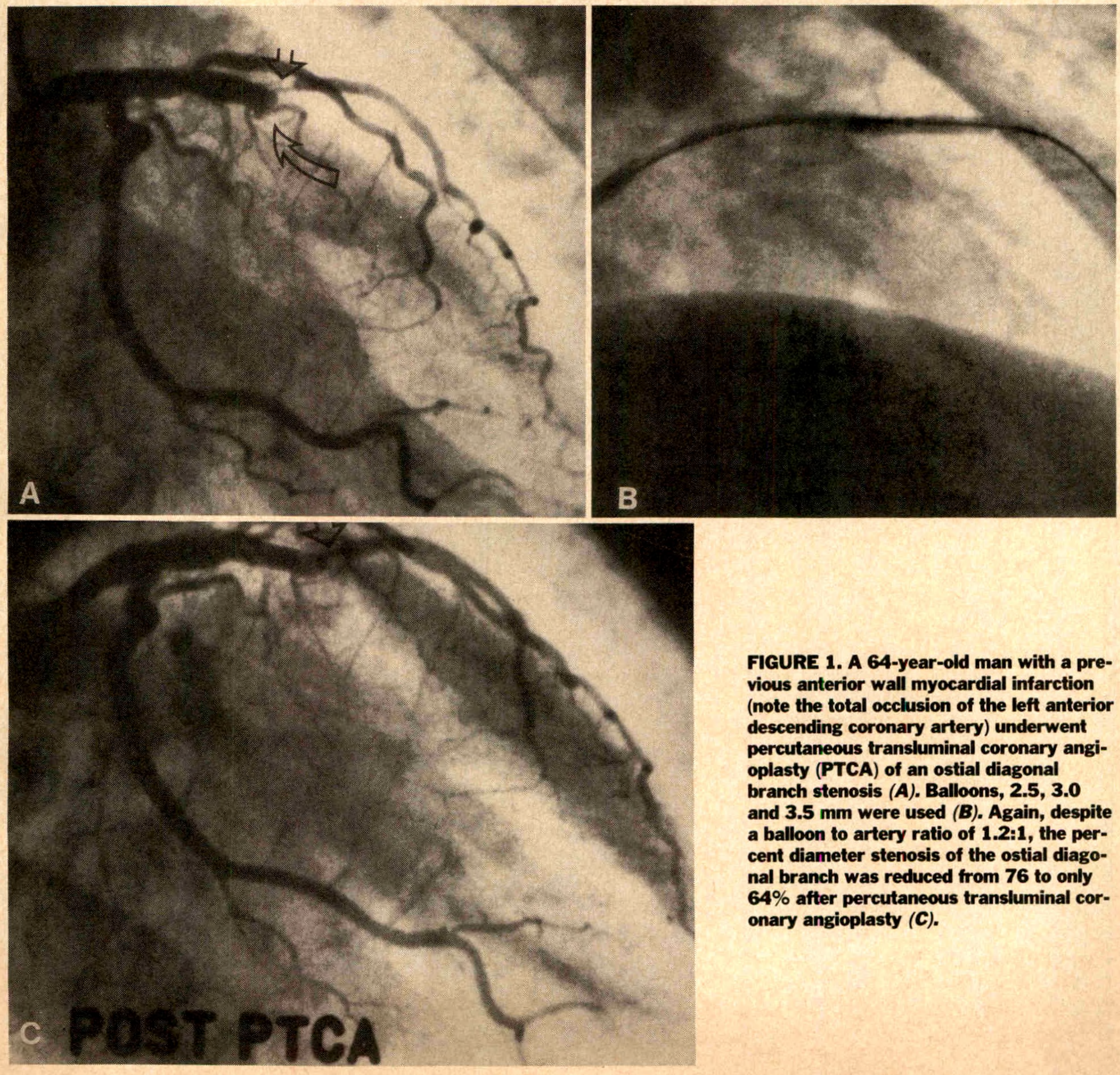

FIGURE 1. A 64-year-old man with a previous anterior wall myocardial infarction (note the total occlusion of the left anterior descending coronary artery) underwent percutaneous transluminal coronary angioplasty (PTCA) of an ostial diagonal branch stenosis *(A)*. Balloons, 2.5, 3.0 and 3.5 mm were used *(B)*. Again, despite a balloon to artery ratio of 1.2:1, the percent diameter stenosis of the ostial diagonal branch was reduced from 76 to only 64% after percutaneous transluminal coronary angioplasty *(C)*.

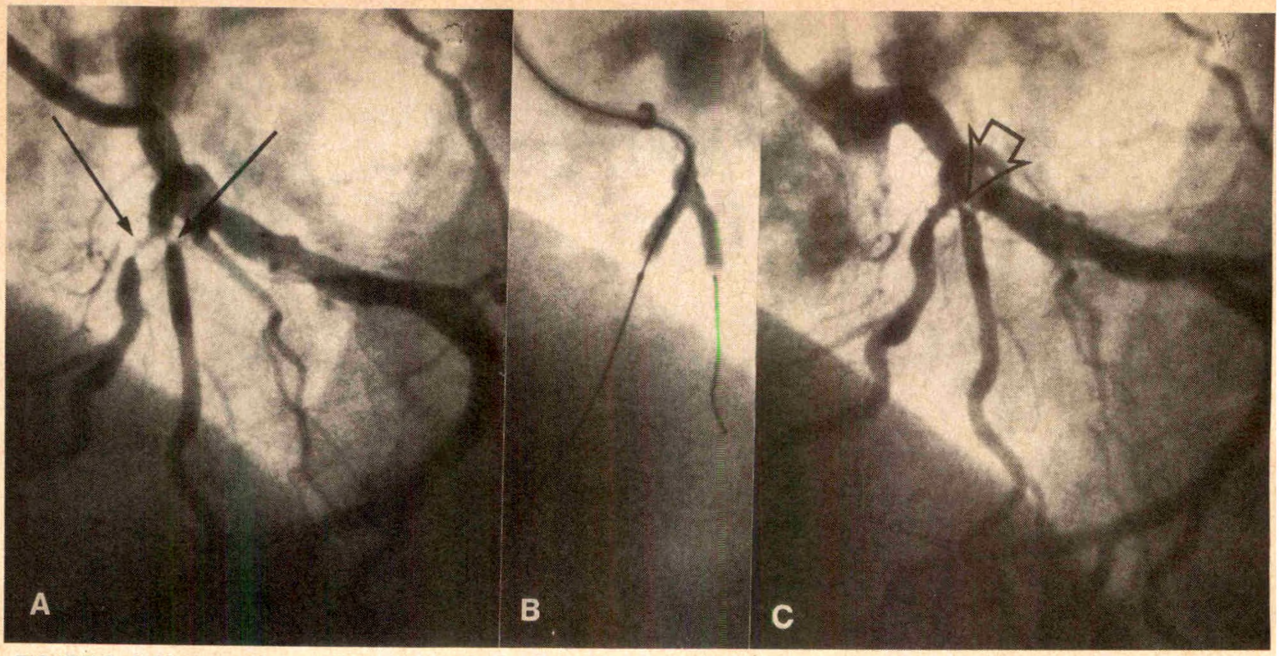

FIGURE 2. A 69-year-old man with postinfarction angina after an anterior wall myocardial infarction underwent coronary angioplasty of a bifurcation stenosis involving the left anterior descending coronary artery and ostial diagonal branch *(A)*. A 3.5-mm balloon in the left anterior descending artery was simultaneously inflated with a 2.5-mm fixed wire device in the diagonal branch *(B)*. Although the percent diameter stenosis in the left anterior descending artery was reduced from 86 to 13%, the percent diameter stenosis in the diagonal branch was reduced from 80 to only 60% after percutaneous transluminal coronary angioplasty *(C)*.

ses associated with bifurcation lesions are shown in Figures 1 and 2.

Follow-up (mean 7.8 ± 5.9 months) was available in all patients. Of the 88 stenoses that were successfully dilated, repeat coronary arteriography was performed in 19 patients (22%). A patent ostial segment was present in 6 patients and restenosis was present in 13 patients. Repeat coronary angioplasty was performed in 12 patients, with a technical success of 75%. Clinical follow-up in this cohort of patients is difficult to evaluate owing to the presence of multivessel disease in 85% of the patients. Nonetheless, chest pain was eliminated or improved in 72% of the patients, 2 patients required coronary bypass surgery, and only 2 patients had a myocardial infarction during the follow-up period.

DISCUSSION

PTCA of stenoses at the ostium of a branch coronary artery results in decreased procedural success despite adequate balloon sizing and increased in-hospital complications when compared with our general population of patients undergoing PTCA. Our findings are similar to those reported with ostial disease involving the renal,[10] the right coronary,[1] and the left anterior descending coronary arteries.[2] These studies have suggested that angioplasty for ostial disease is associated with decreased technical success, more complications and increased restenosis. Sos et al[10] demonstrated that, despite guidewire passage and adequate balloon sizing and inflations, angioplasty of ostial renal artery stenoses resulted in a 10 to 20% success rate versus 75% for nonostial disease. Topol et al[1] showed that PTCA of ostial right coronary artery stenoses produced reduced success rates and increased complications when compared with nonostial lesions. Several studies have also suggested increased restenosis in patients with coronary ostial disease.[2,3] It would appear that an ostial stenosis, regardless of its location in the vascular system, has unique properties that make it resistant to or unfavorable for angioplasty. Previous reports have demonstrated that side branch occlusion during coronary angioplasty occurs in 14 to 17% of cases, particularly in branches with preexisting ostial disease.[11-13] Because of this, various techniques have been proposed for coronary angioplasty of bifurcation stenoses such as double-wire and double-balloon techniques with successive or simultaneous balloon inflations.[4-9] Angioplasty success in these studies was determined by the outcome of the major epicardial vessel and not the branch vessel. In fact, the percent diameter stenosis before and after PTCA has not been reported for the branch vessel in any of these studies. Our data indicate that, although these techniques are useful in preserving side branch patency, they do not appear to improve the technical success of ostial branch coronary angioplasty, nor do they prevent subsequent ischemic complications of the branch vessel.

The presence of significant residual stenosis in ostial branch lesions after angioplasty despite adequate balloon sizing suggests that the primary mechanism responsible for technical failure is elastic recoil. Clearly defined regions of high and low wall shear stress are created at the apex of bifurcations and in the proximal branches.[14] This increased shear stress at branch points may lead to an increase in elastic tissue, and account for elastic recoil after balloon inflations. To overcome this elastic recoil, balloon oversizing has been used in the

hope of optimizing results of PTCA. This strategy may lead to an increase in complications. Specific revascularization strategies for patients with ostial branch disease should take into account these findings. Finally, newer therapeutic procedures such as coronary atherectomy, stents and laser should be evaluated as a potential measure to improve the treatment of ostial branch coronary artery disease.

Acknowledgment: We thank Ellen Sawicki, RN, BS, for data collection, Lori Kilber, BS, for data entry, Howard Liang, MS, for statistical analysis, and Denise Evans for her assistance in preparation of this manuscript.

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Pericardial Effusion After Intravenous Recombinant Tissue-Type Plasminogen Activator for Acute Myocardial Infarction

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The effect of thrombolytic therapy on the frequency, time course and sequelae of pericardial effusion after myocardial infarction are unknown. A prospective, serial, 2-dimensional echocardiographic study of patients with myocardial infarction who received recombinant tissue-type plasminogen activator (rt-PA) was undertaken to address this issue. The study population comprised 52 of the 112 patients enrolled in the first Thrombolysis and Angioplasty in Myocardial Infarction trial at Duke University Medical Center. Enrollment in the serial echocardiography protocol was determined by equipment and support staff availability. Complete echocardiographic studies were performed within 90 minutes after initiation of thrombolytic therapy (day 0), and on days 1, 3 and 6. Patients undergoing serial echocardiography did not differ in demographic or clinical characteristics from those who did not. Pericardial effusion was present in 3 of 38 patients (8%) at day 0, in 2 of 44 (5%) at day 1, in 8 of 43 (19%) at day 3, and in 10 of 42 (24%) at day 6. By day 6, 3 of 10 pericardial effusions were moderate in size, 1 of 10 was large and the remainder were small. No patients developed echocardiographic or hemodynamic signs of cardiac tamponade. The prevalence and time course of pericardial effusion among patients with acute myocardial infarction who received rt-PA in this study are similar to observations reported in earlier studies in which patients did not receive thrombolytic therapy. Adverse sequelae of pericardial effusion after thrombolytic therapy are rare.

(Am J Cardiol 1991;67:496–500)

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Pericardial effusion has been reported to develop in up to one-third of patients in the first week after acute myocardial infarction.[1-4] Despite this frequency, serious clinical sequelae of pericardial effusions after myocardial infarction are rare.[1-3] Recent studies have not shown an important effect of conventional anticoagulant therapy on the frequency or consequences of such effusions.[1-3] However, several cases of hemodynamically significant hemopericardium after anticoagulant therapy (even in the absence of free wall rupture) have been reported.[5-8]

Thrombolytic therapy has recently become standard care for patients with acute myocardial infarction.[9] One recent observational study suggested that urokinase therapy does not increase the prevalence of pericardial effusion evident on day 3.[4] However, there are no other data describing the effects of thrombolytic therapy on the frequency and sequelae of pericardial effusion after thrombolytic therapy. To address this issue, we conducted a prospective, serial, 2-dimensional echocardiographic study of patients with acute myocardial infarction who received intravenous recombinant tissue-type plasminogen activator (rt-PA).

METHODS

Patients: Subjects were drawn from patients with acute myocardial infarction who entered the first Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-I) trial at Duke University Medical Center. The TAMI-I protocol has been described previously.[10] Briefly, all patients received rt-PA at entry. Coronary angiography was performed 90 minutes after initiation of thrombolytic therapy. Patients with a patent infarct-related artery (Thrombolysis in Myocardial Infarction [TIMI] flow grade 2 or 3) were randomized either to immediate coronary angioplasty or to deferred angioplasty at day 7. Patients with persistent occlusion in the infarct-related artery (TIMI flow grade 0 or 1) were not randomized and underwent immediate angioplasty if technically and clinically appropriate.[10]

Thrombolytic and anticoagulant therapy: Patients received a total dose of 150 mg of intravenous rt-PA administered over 6 to 8 hours (10% as a bolus with a total of 60 mg or 1 mg/kg given over the first hour). Patients randomized to immediate angioplasty received a heparin bolus of 5,000 U. All patients received 500 to 1,000 U of intravenous heparin per hour (to keep the partial thromboplastin time 1.5 to 2 times control) for

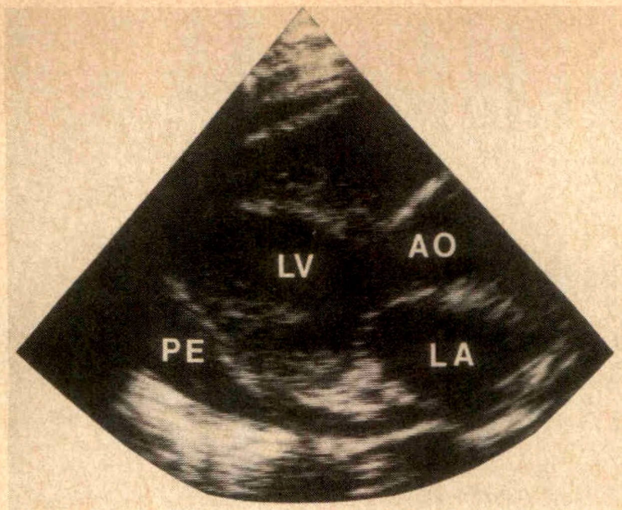

FIGURE 1. Parasternal long-axis view of a posterior echo-free space corresponding to pericardial effusion (PE). AO = aorta; LA = left atrium; LV = left ventricle.

≥24 hours. All patients also received 325 mg of oral aspirin and 75 mg of oral dipyridimole 3 times per day.

Echocardiography: Serial echocardiography was performed on patients entering the TAMI-I study at Duke, as permitted by equipment and support staff availability. Echocardiography was scheduled for immediately after initiation of rt-PA (day 0), and on days 1, 3 and 6 after entry. All studies were performed with a Hewlett-Packard phased-array echocardiographic system. Each study comprised a complete 2-dimensional examination with a 2.5-MHz transducer. Echocardiograms were read in consensus by 2 experienced observers. Studies were read out of sequence and with readers blinded to patient identity and clinical data.

Diagnostic criteria: The echocardiographic diagnosis of pericardial effusion required the presence of an echo-free space posterior to the left ventricle on the parasternal long- and short-axis views throughout the cardiac cycle (Figure 1). We carefully differentiated this finding from descending aorta, pleural effusion, left ventricular pseudoaneurysm and other causes of false-positive diagnosis. The presence of an anterior echo-free space alone was not deemed sufficient to make the diagnosis of pericardial effusion, because of the poor specificity of this finding.[11] No echocardiographic technique accurately determines the volume of a pericardial effusion.[11] However, an attempt was made to quantitate approximately the magnitude of the pericardial effusion. The effusion was considered small if the greatest depth of the echo-free space posterior to the left ventricle was ≤0.5 cm, moderate if >0.5 cm and ≤1.5 cm, and large if >1.5 cm.

When pericardial effusion was demonstrated, studies were examined for echocardiographic evidence of cardiac tamponade, i.e., early diastolic right ventricular collapse and late diastolic or early systolic right atrial collapse.[12,13]

Left ventricular systolic function was assessed echocardiographically using a previously described regional wall motion grading system and a semiquantitative wall motion index.[14] Briefly, the left ventricle was divided into 13 segments, using the 6 standard echocardiographic views. Wall motion in each segment was graded visually for degree of endocardial thickening and inward motion: 1 = normal, 2 = mild/moderate hypokinesia, 3 = severe hypokinesia or akinesia, 4 = dyskinesia. Segments in which <50% of the endocardial surface could be visualized in any view were excluded. A wall motion index was calculated as the sum of segment scores divided by the number of segments adequately visualized.

TABLE I Comparison of Patients Who Underwent Echocardiography Versus Patients Who Did Not

	Echocardiography (n = 52)	No Echocardiography (n = 60)
Men/women (%)	44 (85)/8 (15)	47 (78)/13 (22)
Age (yr)	53 ± 10	55 ± 10
Pain duration (hours)	3.2 ± 1.1	3.3 ± 1.1
AMI location		
Anterior (%)	21 (40)	25 (41)
Inferior (%)	31 (60)	35 (59)
Infarct artery		
Left anterior descending (%)	21 (40)	25 (41)
Left circumflex (%)	10 (19)	8 (14)
Right (%)	21 (40)	28 (46)
TIMI grade at 90 minutes		
0 (%)	15 (29)	13 (22)
1 (%)	3 (6)	5 (8)
2 (%)	11 (21)	8 (13)
3 (%)	23 (44)	34 (57)
IRA patency + Rx group		
Closed, acute PTCA (%)	14 (27)	15 (25)
Closed, no acute PTCA (%)	1 (2)	1 (2)
Open, randomized acute PTCA (%)	17 (33)	12 (20)
Open, randomized deferred PTCA (%)	8 (17)	19 (32)
Open, not randomized (%)	11 (21)	13 (22)
Reocclusion (%)	7 (14)	9 (15)
CABG		
Emergent (%)	3 (6)	1 (2)
Urgent (%)	0	3 (5)
Elective (%)	3 (6)	8 (13)
Death (%)	3 (6)	4 (7)

AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; IRA = infarct-related artery; PTCA = percutaneous transluminal coronary angioplasty; Rx = treatment; TIMI = Thrombolysis in Myocardial Infarction.

RESULTS

Patient characteristics: Fifty-two of the 112 patients entering the TAMI-I trial underwent serial echocardiography: 38 patients had a complete baseline (day 0) study, and 44, 43 and 42 had complete echocardiographic studies on days 1, 3 and 6, respectively. Overall, complete studies were possible on all 4 days for 36 patients, on 3 of 4 days for 15 patients and on 2 days for 1 patient.

Characteristics of the patients who underwent serial studies are compared with those who did not in Table I. The group who underwent serial echocardiography did not differ importantly from those who did not in demographic features, infarct location or TIMI grade 90 minutes after rt-PA infusion. On the other hand, a high-

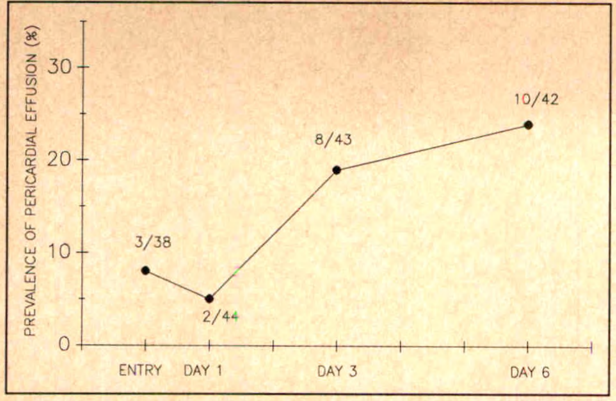

FIGURE 2. Percentage of patients undergoing echocardiography who were found to have a pericardial effusion acutely (day 0) and on days 1, 3 and 6. Numbers of patients with effusion *(numerator)* and number with an adequate echocardiographic study *(denominator)* on each day are shown.

er proportion of patients who did undergo serial echocardiography underwent immediate angioplasty. Nevertheless, the proportion ultimately leaving the catheterization laboratory with a patent infarct-related artery was the same (98%) for each group, whether accomplished through emergency angioplasty or solely through thrombolytic therapy. Table I also compares the frequency of clinical events between patients who did and did not undergo serial echocardiography. Although small differences are present, patients included in the echocardiographic portion of this study appear generally representative of the trial population enrolled in TAMI-I.

Pericardial effusion: Figure 2 shows the prevalence of pericardial effusion on each day of the study. At the time of the acute study (i.e., within 90 minutes of rt-PA infusion), 3 of 38 patients (8%) were noted to have pericardial effusion. Over the subsequent week, the prevalence of patients with pericardial effusion increased, and by day 6, 10 of 42 (24%) had 2-dimensional echocardiographic evidence of pericardial effusion.

All pericardial effusions noted acutely (day 0) and on days 1 and 3 were small. On day 6, 6 of 10 pericardial effusions were small, 3 of 10 were moderate and only 1 was large. No patient had or subsequently developed clinical signs of tamponade.

Clinical findings in patients with and without pericardial effusion are shown in Table II. Patients with pericardial effusion were more often female. Anterior infarctions were slightly more frequent in patients with effusions, although the echocardiographic wall motion index did not differ at baseline or on day 6. The in-hospital death rate was not significantly different between the 2 groups, although there was a trend toward lower mortality in the effusion group. The 2 groups were otherwise similar.

TABLE II Characteristics of Patients With and Without Pericardial Effusion

	Pericardial Effusion (n = 15)	No Pericardial Effusion (n = 37)
Male (%)	10 (67)	34 (92)
Age (yr)	56 ± 11	55 ± 10
AMI location		
Anterior (%)	7 (47)	14 (38)
Inferior (%)	8 (53)	23 (62)
TIMI grade at 90 minutes		
0 (%)	5 (33)	10 (27)
1 (%)	1 (7)	2 (5)
2 (%)	4 (27)	7 (19)
3 (%)	5 (33)	18 (49)
IRA patency + Rx group		
Closed, acute PTCA (%)	5 (33)	9 (24)
Closed, no acute PTCA (%)	0	1 (3)
Open, randomized acute PTCA (%)	4 (27)	13 (35)
Open, randomized deferred PTCA (%)	4 (27)	5 (14)
Open, not randomized (%)	2 (13)	9 (24)
Wall motion index (mean ± SD)		
Baseline	1.57 ± 0.42	1.68 ± 0.48
Day 6	1.47 ± 0.38	1.43 ± 0.41
In-hospital death (%)	0	3 (8)

SD = standard deviation; other abbreviations as in Table I.

DISCUSSION

This report describes the first prospective serial echocardiographic study of pericardial effusion in patients with acute myocardial infarction who received thrombolytic therapy. Pericardial effusion was found frequently in this group, occurring in 24% within the first week after infarction.

This study is limited by the lack of a control group who were not receiving thrombolytic therapy. Such patients were rare at Duke Medical Center during the period in which this study was performed. For this reason, comparison with previously published studies in conservatively treated patients is necessary.

Comparison with previous studies: The frequency and time course of pericardial effusion noted here is similar to findings of several studies in which patients did not receive thrombolytic therapy. Pierard et al[1] found effusions in 26% of patients, using serial 2-dimensional echocardiography in the first week after infarction. Galve et al[2] found effusions in 25% of patients 3 days after infarction and in 21% at 10 days, using M-mode techniques. Recently, Sugiura et al[4] reported a 25% prevalence of pericardial effusion at day 3 after myocardial infarction. A somewhat higher prevalence of 37% was detected by Kaplan et al[3] with M-mode echocardiography. All effusions occurred by day 5. In contrast, Wunderink[15] found effusions in only 5.6% of patients within the first 3 days after myocardial infarction.

The peak prevalence of 24% found in the present study is similar to figures reported by Pierard, Galve, Sugiura and their co-workers, but differs from the values reported by Kaplan et al and Wunderink. Part of this disparity may represent technique. Both of these latter studies used M-mode echocardiography, whereas the present report details findings with 2-dimensional echocardiography. M-mode may be superior in detecting very small effusions, because of increased axial resolution,[11,16] although such small effusions are generally not clinically important. Other factors may importantly

limit both the sensitivity and specificity of M-mode echocardiography in the diagnosis of pericardial effusion.[11] This technique may be underinclusive, because only a limited region of the heart is visualized. It could also be overinclusive, because contiguous structures such as the aorta, pleural fluid and subepicardial adipose may not be easily distinguished from pericardial effusion with M-mode echocardiography. These factors may in part explain the noted disparities. Additionally, Wunderink did not obtain echocardiograms after day 3 from patients who did not have effusions by that time and thus may have underestimated the prevalence relative to studies, such as ours, with longer follow-up.

Effects of systemic anticoagulation and thrombolytic therapy: Several recent studies retrospectively examined the effect of systemic anticoagulation on pericardial effusion formation. Galve et al[2] found no difference between patients treated with full- and low-dose heparin. Pierard et al[1] and Wunderink[15] found no difference in the frequency of systemic anticoagulation among patients with and without pericardial effusion. In a study of postmyocardial infarction patients with pericardial effusion who were treated with systemic anticoagulation for left ventricular thrombus, no patient developed an enlarged pericardial effusion.[17] On the other hand, Guberman et al[8] described 5 acute myocardial infarction patients who received bolus heparin therapy and developed acute hemorrhagic tamponade within the first few days of presentation. The total number of acute myocardial infarction patients from which these 5 were drawn was not reported. From a review of earlier reports, however, Chalmers et al[18] concluded that anticoagulation in acute myocardial infarction patients does not increase the risk of hemorrhagic tamponade.

No previous studies have prospectively evaluated pericardial effusion formation with serial echocardiography in the setting of thrombolytic therapy. In an early series reviewed retrospectively for such effects, 4 patients were noted to have received streptokinase (route of administration unspecified); 1 of 4 developed an effusion.[15] More recently, Sugiura et al[4] studied 330 consecutive patients with acute Q-wave myocardial infarction, 103 of whom received intravenous or intracoronary urokinase. Thirty-three percent of the patients with pericardial effusion on day 3 received urokinase, compared with 31% of patients without an effusion, suggesting that thrombolytic therapy had no effect on the incidence of pericardial effusions developed after acute myocardial infarction.

The apparent lack of effect of systemic anticoagulation or thrombolytic therapy on the rate of development, time course and clinical sequelae of pericardial effusion after acute myocardial infarction is perhaps surprising. Streptokinase therapy in patients mistakenly diagnosed with acute myocardial infarction, who in reality have inflammatory pericarditis, may lead to the development of effusion and even tamponade.[19,20] If the etiology of pericardial effusion after myocardial infarction were indeed inflammatory, anticoagulant or thrombolytic therapy might be expected to lead to similar consequences. In >1,000 patients with acute myocardial infarction treated with thrombolytic therapy in the ongoing multicenter TAMI trials, not 1 case of cardiac tamponade unrelated to cardiac rupture has been observed (R. M. Califf, personal communication, October 1990). Recent reports, however, clearly show a lack of association between postinfarction pericardial effusion and typical pericarditic pain or rub.[2,3,21] In contrast, positive associations have been made between effusion and anterior infarct location, larger infarct size, more severe left ventricular dysfunction, congestive heart failure and ventricular arrhythmias.[1–3] Sugiura et al[4] reported that patients with acute myocardial infarction who had a pericardial effusion on day 3 have higher pulmonary wedge pressures, lower cardiac outputs and more severe wall motion abnormalities than patients with myocardial infarction without an effusion. Available clinical data, then, suggest a hemodynamic etiology for postmyocardial infarction pericardial effusion, which may explain the lack of adverse consequences after systemic anticoagulation or thrombolytic therapy, or both.

Differences between patients with and without pericardial effusion: As has been reported previously, effusions in the present study were more frequent in anterior than inferior infarctions.[1,2] Patients with pericardial effusion were more likely to be female, a finding not previously reported and without clear explanation. Our echocardiographic wall motion index did not differ substantially between those with and without effusions. This differs with the findings of Pierard et al,[1] who reported a more abnormal echocardiographic wall motion index in patients with pericardial effusion. The cause for this disparity is not certain, although some amount of myocardial salvage due to the administration of early thrombolytic therapy may have made such a trend more difficult to detect.

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Comparison of the Efficacy of Questran Light, a New Formulation of Cholestyramine Powder, to Regular Questran in Maintaining Lowered Plasma Cholesterol Levels

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Sixty-one men with known hypercholesterolemia (plasma cholesterol >265 mg/dl), most of whom were previous participants in the Coronary Primary Prevention Trial of the U.S. Lipid Research Clinic Program, were chosen to take part in this study to test the effectiveness of a new low-calorie (Questran® Light) cholestyramine formulation against the proven effectiveness of the currently marketed formulation Questran in maintaining lowered plasma cholesterol levels. The study recorded changes in fasting plasma lipids, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and calculated low-density lipoprotein cholesterol. After establishing baseline lipid/lipoprotein levels in a 3-week period during which all participants received the currently marketed formulation, the men were randomized into 2 groups, 1 group (n = 31) taking the new Questran Light formulation of 4 g of cholestyramine in 5 g of powder per pack, while the other group (n = 30) continued to take the marketed Questran formulation of 4 g of cholestyramine in 9 g of powder per pack. Each group consumed a total of 24 g/day of cholestyramine in 2 divided doses. At the end of the maintenance phase of the study there were no statistically significant mean changes in percentage from baseline to end-point lipid/lipoprotein levels within either group, nor were there any significant differences between the Questran Light group or the currently marketed Questran formulation group. The new low-calorie cholestyramine formulation appears to be equally as effective in maintaining lowered plasma cholesterol levels as the currently marketed formulation.

(Am J Cardiol 1991;67:501–505)

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Elevated plasma cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, have been implicated in the development of atherosclerosis.[1–10] LDL cholesterol reductions by diet and drugs, including bile-acid sequestrants such as Questran®, have reduced coronary artery disease, slowed development, and caused regression of coronary artery lesions.[11–15] Bile-acid sequestrants are drugs of first choice.[16] Poor patient adherence, which may compromise an agent of proven pharmacologic value,[17] may be addressed by reformulation of the medication.

This study examines the effectiveness of a new formulation of cholestyramine powder, with reduced volume and caloric content (Questran Light), to maintain reduced plasma cholesterol levels in hypercholesterolemic men by comparing it with regular Questran.

METHODS

This study's design used initiation with active treatment (phase I), then randomization to test in parallel the 2 formulations (phase II). Sixty-six hypercholesterolemic men were enrolled. Five withdrew and were excluded from analysis because of fatal myocardial infarction,[1] refusing medication,[1] gastritis,[1] constipation[1] and, after a week of the new formulation, constipation and dyspepsia.[1] The 61 remaining men reported here included 2 who completed the 3-week test period and then withdrew: 1 taking regular Questran withdrew because of constipation and hemorrhoids and 1 taking Questran Light withdrew because he refused medication. Forty-nine of the 61 men had participated in the Lipid Research Clinic's Coronary Primary Prevention Trial with good medication adherence.

All subjects were free-living, ostensibly healthy, between the ages of 42 and 68 years, had elevated plasma cholesterol and LDL cholesterol levels in the >95th percentile, and had not received any lipid-altering drugs for 3 months. After completing an informed consent form, medical history and physical examination, counseling was given on medication adherence by proven techniques.[11] They were counseled by conventional clinical practices to maintain the American Heart Association's phase I or II low-fat, low-cholesterol diets that matched closest to their current diets. Three-day food records were scored to evaluate dietary compliance.[18] Other drugs or diet supplements, e.g. fiber, with lipid effects were not allowed. Medications for other medical rea-

TABLE I Mean Baseline Lipid/Lipoprotein Values

	Treatment				
	Original Formulation (n = 30)		New Formulation (n = 31)		
Cholesterol	Mean	SEM	Mean	SEM	p Value*
All Completing Patients					
Total (mg/dl)	237	9.6	226	7.2	0.38
LDL† (mg/dl)	152	9.9	141	6.7	0.38
HDL‡ (mg/dl)	46	1.7	48	1.6	0.48
HDL/total (%)	20	1.0	22	0.8	0.33
Triglycerides (mg/dl)	192	16.2	184	12.6	0.70
	Original Formulation (n = 23)		New Formulation (n = 26)		
Former LRC/CPPT Participants					
Total (mg/dl)	237	8.4	226	6.0	0.29
LDL-C[1] (mg/dl)	149	8.8	140	5.1	0.35
HDL-C[2] (mg/dl)	47	2.1	48	1.9	0.70
HDL/total (%)	20	1.1	22	0.9	0.40
Triglycerides (mg/dl)	202	19.5	188	14.6	0.56

* Significance of 1-way analysis of variance F statistic at 1, 59 degrees of freedom.
† Low-density lipoprotein cholesterol (calculated) = total cholesterol − (HDL + triglycerides/5).
‡ High-density lipoprotein cholesterol.
LRC/CPPT = Lipid Research Clinic/Coronary Primary Preventional Trial; SEM = standard error of the mean.

TABLE II Mean End-Point Lipid/Lipoprotein Values

	Treatment				
	Original Formulation (n = 30)		New Formulation (n = 31)		
Cholesterol	Mean	SEM	Mean	SEM	p Value*
All Completing Patients					
Total (mg/dl)	241	9.6	223	6.7	0.14
LDL† (mg/dl)	155	8.8	141	6.3	0.22
HDL‡ (mg/dl)	45	1.7	47	1.8	0.47
HDL/total (%)	20	1.1	21	0.9	0.20
Triglycerides (mg/dl)	207	17.8	178	14.6	0.21

* Significance of 1-way analysis of variance F statistic at 1, 59 degrees of freedom.
† Low-density lipoprotein cholesterol (calculated) = total cholesterol − (HDL + triglycerides/5).
‡ High-density lipoprotein cholesterol.
Abbreviations as in Table I.

sons were maintained at the same dosage and were recorded.

Phase I, a 3-week baseline period with 3 clinic visits, allowed all subjects to stabilize on regular Questran. Phase II consisted of 4 weeks of randomized testing of 2 parallel treatment groups in which the plasma lipid maintaining efficacy of the new low-calorie formulation of powdered cholestyramine was compared with the regular formulation. Clinic visits occurred after cumulative treatment periods of 1, 3 and 4 weeks, respectively (i.e., study weeks 1, 3 and 4).

The first treatment group continued the regular cholestyramine formulation (Questran) containing 4 g of resin and 5 g of sucrose and excipients totaling 9 g of powder per packet. The second treatment group was given the new formulation (Questran Light) containing 4 g of cholestyramine with aspartame and excipients totaling 5 g of powder per packet. All subjects took 3 packets twice daily, totaling 24 g/day of cholestyramine. The 3 packets were taken within 30 minutes of the morning and evening meals. Compliance was evaluated by packet counts. The caloric content of Questran Light and regular Questran was 1.6 and 14 calories per packet, respectively, producing treatment group difference in caloric intake of 74.4 calories/day. The estimated group difference in calorie intake over 28 days, 2,083 calories, potentially yields an insignificant difference in body weight of 0.27 k (74.4 kcal × 28 days divided by 7,700 kcal/k of adipose tissue).

Laboratory tests were performed at the beginning and the end of the 7-week study: urinalysis, blood count, and a panel of serum biochemical measures (SMAC 13). At each clinic visit, fasting plasma lipids were measured using standardization and quality control under the Centers for Disease Control Lipid Standardization Program: total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, the calculated LDL cholesterol and the ratio of HDL cholesterol to total cholesterol.

Baseline values were defined as the last determinations before randomization. The rationale for not averaging the baseline determinations is explained in the Results section. End-point lipid values were defined as the average of the 2 final determinations at the third and fourth weeks of phase II.[19]

Paired t tests were used to assess changes from baseline to end point for all lipids. Two-sample t tests and analysis of covariance were performed to test the null hypothesis of no difference between treatments in actual change as well as percent change from baseline to end point. Confidence intervals of 90% were used to establish that the new formulation was not substantially less effective than the regular formulation (i.e., within 20%). The approach used is analogous to that used in bioequivalence studies.[20] The Stuart-Maxwell statistic and the Sign test were used to analyze changes from pre- to poststudy laboratory data. Medical history and physical examination data were examined by the chi-square test. Related demographic and dosing information were compared by the 2-sample t test.

RESULTS

Thirty men taking the regular cholestyramine and 31 men taking the new low-calorie cholestyramine completed the study. At baseline, no significant differences between the treatment groups were noted for age, weight, height, blood pressure, race, medical histories, prestudy physical examination or diet scores. The mean durations of phases I and II were 20 and 29 days, respectively. During the comparison of treatments there were no significant differences between the groups in body weight, diet scores, medical history and physical examination data. Adherence to the prescribed medications was high, stable, and not different between the

TABLE III Mean Lipid/Lipoprotein Change from Baseline to End Point

Cholesterol	Treatment: Original Formulation (n = 30) Mean	SEM	New Formulation (n = 31) Mean	SEM	p Value*
All Completing Patients					
Total					
Change (mg/dl)	+4.2	4.3	−2.8	4.7	0.28
Change (%)	+2.2	1.7	−0.6	1.9	0.29
LDL†					
Change (mg/dl)	+2.7	4.0	−0.2	4.8	0.64
Change (%)	+3.4	2.6	+1.2	3.2	0.59
HDL‡					
Change (mg/dl)	−1.4	0.7	−1.3	1.5	0.94
Change (%)	−2.8	1.6	−1.4	3.2	0.70
HDL/total (%)					
Change	−0.8	0.4	−0.3	0.6	0.47
Change (%)	−4.1	2.0	−0.7	2.4	0.30
Triglycerides					
Change (mg/dl)	+14.4	10.3	−6.5	10.8	0.17
Change (%)	+11.4	5.9	−1.0	5.7	0.14

* Significance of 1-way analysis of variance F statistic at 1, 59 degrees of freedom.
† Low-density lipoprotein cholesterol (calculated) = total cholesterol − (HDL + triglycerides/5).
‡ High-density lipoprotein cholesterol.
Abbreviations as in Table II.

TABLE IV 90% Confidence Intervals for Differences in Percent Change Between Intervals

Cholesterol	90% Confidence Limits for New Formulation Minus Original Formulation: Lower Limit (%)	Upper Limit (%)
All Completing Patients		
Total	−7.19	1.57*
LDL†	−9.07	4.65*
HDL‡	−4.65*	7.41
HDL/total	−2.01*	8.65
Triglycerides	−26.16	1.40*

* These values bound the extent to which the new formulation could be worse than the currently marked formulation, with 90% confidence.
† Low-density lipoprotein cholesterol (calculated) = total cholesterol − (HDL + triglycerides/5).
‡ High-density lipoprotein cholesterol.

treatment groups for weeks 1, 3 and 4 (mean 91.4% with Questran Light and 93.1% with regular Questran). The groups' mean adherences during baseline were at study week −1, 70 and 76%; and study week 0, 85 versus 93%, this latter intergroup difference with p = 0.05. Transient adverse events were reported 7 times in each treatment group and were not different from those previously reported for regular Questran.

The 2 treatment groups demonstrated no significant differences in the mean baseline plasma concentrations of total, HDL, LDL and triglyceride levels, and the HDL/total cholesterol levels, and these findings were not altered by inclusion of nonparticipants in the Coronary Primary Prevention Trial (Table I). All subjects demonstrated decreases in LDL and total cholesterol from screening levels to baseline levels. The mean end-point lipid values of the 2 treatment groups were quite similar (Table II).

The comparisons of the 2 formulations were based on comparison of the changes from baseline to end-point lipid values for both treatment groups, and the absolute and percent changes (Table III). There were no statistically significant differences between the 2 groups for any of the lipid values. However, all of the changes from baseline to end point favored the new over the regular formulation.

The absence of a statistically significant difference does not necessarily imply equivalence. The power of the statistical tests, or confidence intervals, must also be considered. Table IV lists 90% confidence intervals for the differences between the 2 formulations with respect to percent change. The intervals are constructed around

TABLE V Plasma Lipids—Mean Lipid Values* by Visit

Study Week	Cholesterol	HDL Cholesterol	Calculated LDL†	HDL Total Cholesterol	Triglycerides
Old Formulation					
−3	271.8	46.8	189.3	17.9	178.7
−1	239.2	45.0	155.7	19.5	192.1
0	236.8	46.3	152.0	20.4	192.5
1	230.1	45.5	147.0	20.5	188.3
3	241.6	44.9	155.2	19.4	207.6
4	239.1	44.9	152.8	19.8	206.5
New Formulation					
−3	271.0	46.4	190.7	17.8	169.3
−1	240.0	47.1	157.0	20.5	179.9
0	226.3	48.0	141.4	21.6	186.5
1	220.0	46.4	139.3	21.5	171.5
3	225.9	46.5	140.9	21.1	192.5
4	220.7	46.8	140.9	21.6	164.9

* mg/dl.
† See Figure 1.
HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

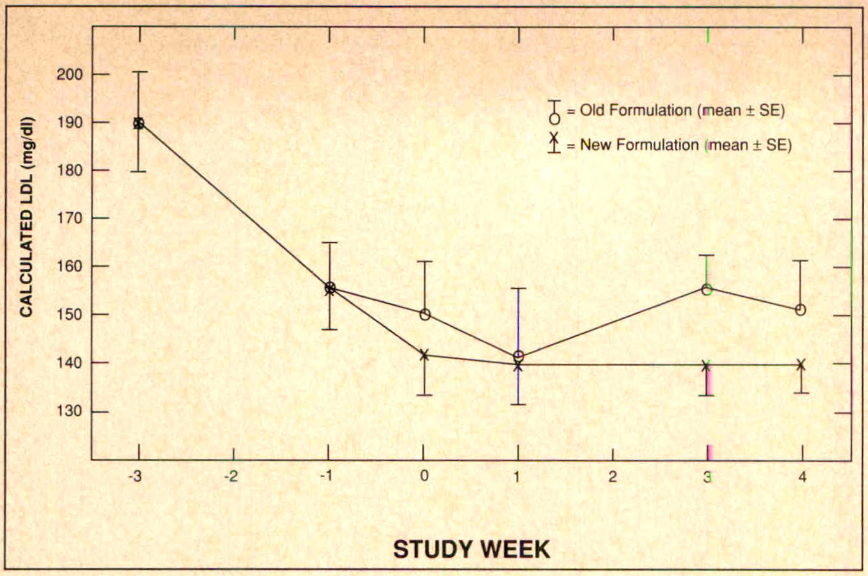

FIGURE 1. Effect of Questran Light and regular Questran on calculated plasma low-density lipoprotein (LDL) levels. Values are means ± standard error (SE) of the mean of average of determinations in weeks 3 and 4 of 4-week study.

the difference, new minus old. Large positive differences in total and LDL cholesterol or triglyceride levels would imply superiority of the regular formulation. Large negative differences in HDL or HDL/total cholesterol would also imply superiority of the regular formulation. The values marked with an asterisk in Table IV show that from this study one can be 90% confident that the new formulation is not substantially less effective than the regular formulation on all of these parameters. These values might actually imply a slight superiority for the new formulation over the regular formulation, although there is not a statistically significant difference.

The mean lipid values by study weeks for the 2 groups demonstrate the prompt reduction of cholesterol levels by cholestyramine (Table V). However, the new low-calorie formulation (Questran Light) apparently exhibits a slight advantage. Figure 1 suggests that LDL cholesterol values were stabilized by study week −1 in the group that was later randomized to the original formulation, but not until study week 0 in the group later randomized to the new formulation. For this reason, baseline was defined as the study week 0 determinations rather than the average of the study week −1 and 0 determinations.

The clinical laboratory tests showed no significant differences before or after the distribution of values and in the number of positive and negative changes and showed no trends in change.

The adverse experiences reported were not remarkably different than previously reported for Questran, consisting almost exclusively of gastrointestinal disturbances. During phase II of the study, 8 of 31 patients (26%) reported adverse experiences with the regular formulation, compared with 6 of 32 patients (19%) with the new formulation. This difference is not significant.

DISCUSSION

This study demonstrates that the efficacy of the new formulation of cholestyramine (Questran Light) is equivalent to the efficacy of the regular formulation of Questran in maintaining Questran-induced reduction of LDL cholesterol. The new formulation shows the same primary lipid alteration repeatedly demonstrated with regular cholestyramine, i.e., reduction in plasma LDL cholesterol. With high and stable adherence to the medications, there were no adverse experiences different from those previously reported for Questran.

Although trends for lower LDL and higher HDL cholesterol between the 2 treatment groups appear evident at the end of the baseline period, and prior to randomization, such group differences, if true, would not influence the end-point measure of this study. The end-point measure for each lipid evaluated the treatment effect for each subject individually, i.e., the difference between the lipid level at baseline and the mean level after 3 and 4 weeks of test treatment.

Significant practical advantages for Questran Light have been achieved by the new formulation. A consumer preference for Questran Light has been reported.[21] A test panel preferred Questran Light over regular Questran when mixed with water or orange juice, 77 and 80%, respectively. It was rated higher using a hedonic scale including flavor, consistency, mouth feel and aftertaste. It is less bulky to carry, and the volume of liquid required for suspension is half that of regular Questran. Dosing twice a day is realistic. The reduction in caloric content has reduced its potential for impairing weight control.

The equal lipid efficacy of the Questran Light, and the sensory preference for it, has clinical significance for physicians treating hypercholesterolemia, because bile-acid sequestrants, including cholestyramine, have been recommended as first choice lipid-altering agents owing to safety and efficacy.[16] Cholestyramine therapy has reduced progression of atherosclerotic lesions.[13] The bile-acid sequestrants in combination therapies have caused regression of coronary lesions of atherosclerosis.[14,15] Facilitating the clinical use of cholestyramine by the formulation as Questran Light makes bile-acid sequestrant

therapy more accessible to the practicing physician for controlling hypercholesterolemia in the treatment and prevention of atherosclerosis.

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Characteristics of Accessory Pathways Exhibiting Decremental Conduction

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The prevalence, electrophysiologic characteristics and functional significance of decremental conduction over an accessory pathway were examined in this retrospective study of 653 patients who had an accessory pathway demonstrated at electrophysiologic study. Decremental conduction was identified in 50 patients (7.6%). In 15 patients with anterograde decremental conduction, the accessory pathway was right parietal or septal in 14 patients and left parietal in 1 patient. In the 40 patients with retrograde decrement, the accessory pathway was left parietal in 19, posteroseptal in 13, right parietal in 2 and right anteroseptal in 6 patients. Anterograde conduction over the accessory pathway was absent in 11 of the 40 patients with retrograde decrement. Retrograde conduction over the accessory pathway was absent in 9 patients with anterograde decrement. There was no significant difference in the accessory pathway effective refractory period, or shortest cycle length with 1:1 conduction over the accessory pathway in anterograde and retrograde directions. The shortest RR interval in atrial fibrillation between 2 preexcited QRS complexes was longer in patients wih anterograde decremental conduction than in a control group of patients with anterograde-conducting accessory pathways without decremental properties.

These data demonstrate that decremental conduction over accessory pathways is uncommon. Anterograde decremental conduction usually occurs in right-sided or septal pathways that often do not conduct in the retrograde direction.

(Am J Cardiol 1991;67:506–510)

From the Cardiac Investigation Unit, University Hospital, University of Western Ontario, London, Canada. This study was supported in part by the Heart and Stroke Foundation of Ontario, Toronto, Canada. Dr. Klein is a Distinguished Research Professor of the Heart and Stroke Foundation of Ontario. Manuscript received June 5, 1990; revised manuscript received October 29, 1990, and accepted October 31.

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Conduction velocity over an accessory pathway is typically rate-independent, with ventriculoatrial or atrioventricular conduction time remaining constant during incremental pacing and extrastimulus testing.[1–3] This electrophysiologic feature helps distinguish accessory pathway conduction from atrioventricular nodal conduction. Rate-dependent prolongation of accessory pathway conduction has been described in a small number of patients and both continuous and discontinuous conduction curves have been identified.[4–10]

This retrospective study defines the prevalence of rate-dependent accessory pathway conduction in 653 patients with accessory pathways, describes the electrophysiologic characteristics of accessory pathways exhibiting rate-dependent conduction, and assesses the functional significance of anterograde decremental conduction.

METHODS

Patients: Between 1981 and 1989, 653 patients with an accessory pathway underwent electrophysiologic study at University Hospital. Patients who were identified as having decremental accessory pathway conduction, as defined later, were evaluated.

Electrophysiologic study procedure: The method of study has been described in detail elsewhere.[7] Briefly, after obtaining written, informed consent, patients had multipolar electrode catheters positioned under local anaesthetic at the high right atrium, right ventricular apex, His recording position and the coronary sinus. The coronary sinus catheter consisted of a quadripolar catheter with 1 cm of electrode spacing. Unipolar electrograms were obtained from each of the poles of the coronary sinus catheter and filtered from 0.05 to 400 Hz. Bipolar electrograms were also obtained from paired coronary sinus, right atrial, right ventricle and His catheter electrodes and filtered at 40 to 400 Hz. Stimulation consisted of right atrial and right ventricular extrastimulus testing and incremental pacing. The electrophysiologic study was recorded on magnetic tape. The taped electrophysiologic study recordings were replayed on a Siemens 16-channel mingograph chart recorder at paper speed 100 mm/s.

Anterograde conduction properties: After atrial extrastimulus testing and atrial incremental pacing, intracardiac intervals were measured and plotted graphically (Figure 1, A and B). The atrial and ventricular electrograms measured were those recorded closest to the origin of the accessory pathway.

Retrograde conduction properties: After ventricular extrastimulus testing and incremental pacing, intracardiac intervals were measured and plotted graphically. Again, the intervals between atrial and ventricular electrograms closest to the accessory pathway were measured.

Control population: To compare locations of accessory pathways and the functional significance of anterograde decrement, patients with decremental accessory pathways were compared with 163 consecutive patients with accessory pathways without decremental conduction undergoing electrophysiologic study between January 1988 and January 1990.

Definitions: Decremental accessory pathway conduction was considered present if the following criteria were satisfied: (1) There was rate-dependent prolongation of ventriculoatrial or atrial-delta wave intervals by >30 ms as measured in the electrograms nearest the accessory pathway, or (2) Wenckebach anterograde or retrograde block could be demonstrated over the accessory pathway (Figure 2). In addition, evidence for the decrement occurring over the accessory pathway as opposed to the normal conducting system was considered to be persistence of a delta wave (anterograde) and eccentric retrograde atrial activation, with decrement occurring at the site of the shortest ventriculoatrial interval (retrograde). In the case of septal accessory pathways where retrograde conduction could be confused with retrograde atrioventricular nodal conduction, progressive decrement after induction of nonpreexcited atrioventricular reentrant echo cycles or tachycardia was considered to occur over the accessory pathway. Also, prolongation of the ventriculoatrial interval after ventricular extrastimuli delivered during atrioventricular reentrant tachycardia at a time when the His bundle was refractory and without change in the retrograde ac-

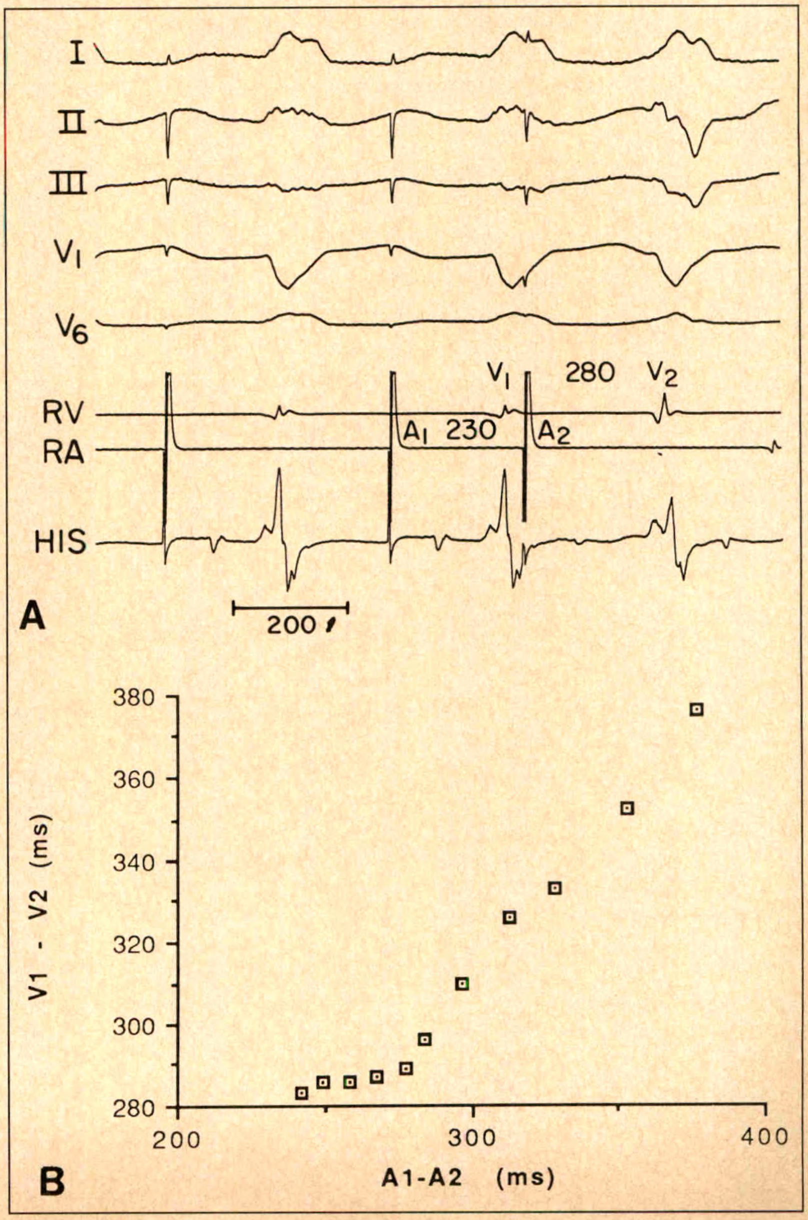

FIGURE 1. ***A,*** **right atrial (RA) extrastimulus testing in a patient with a right parietal accessory pathway. Note that the V_1-V_2 interval is 50 ms longer than A_1-A_2 interval. Preexcitation is still present after the atrial extrastimulus. The delta wave to delta wave interval in this patient is identical to the V_1-V_2 interval. Five surface leads (I,II,III,V_1,V_6), right ventricular (RV), right atrial and His bundle (His) recordings are shown.** ***B,*** **graph of local A_1-A_2 interval (ms) versus V_1-V_2 intervals measured during right atrial extrastimulus testing in the same patient. The nonlinear relation indicates anterograde decrement over the accessory pathway. A = atrial electrogram; V = ventricular electrogram.**

tivation sequence was considered to occur over the accessory pathway.

Statistical analysis: Continuous variables were compared using the unpaired Student's *t* test. Accessory pathway locations in control and study populations were compared with an exact 3 by 4 table test. Results were considered statistically significant if the p values (2 tailed) were <0.05.

RESULTS

Decremental accessory pathway conduction was identified in 50 patients (7.6%). There were 29 men and 21 women (mean age ± standard deviation 36 ± 14 years, range 13 to 68). The presentation in these patients was with atrioventricular reciprocating tachycardia (19 patients), atrial fibrillation (9 patients), atrial fibrillation and atrioventricular-reciprocating tachycardia (5 patients), permanent form of junctional reciprocating tachycardia (6 patients), palpitations (5 patients) and palpitations and syncope (1 patient). Five patients were asymptomatic and studied as part of an ongoing natural history study.[11] The clinical tachycardia was induced in all patients at electrophysiologic study. Patients with atrioventricular reentry all had ventriculoatrial intervals of <160 ms apart from the patients with the permanent form of junctional reciprocating tachycardia in whom the ventriculoatrial intervals ranged from 175 to 360 ms (mean 276 ± 64).

Decremental conduction was present in an anterograde direction only in 10 patients, retrograde direction only in 35 patients and in both directions in 5 patients. Decremental conduction was greatest during extrastimulus testing in 41 patients and during incremental pacing in 9 patients.

Patients with anterograde decremental conduction (Table I): The shortest cycle length maintaining 1:1 anterograde conduction over the accessory pathway was 326 ± 57 ms and the anterograde accessory pathway effective refractory period was 281 ± 42 ms. Retrograde conduction over the accessory pathway could not be demonstrated in 9 of the 10 patients. The retrograde accessory pathway effective refractory period was <255 ms and the shortest cycle length with 1:1 conduction over the accessory pathway was 340 ms in the remaining 1 patient with intact retrograde conduction. The maximal prolongation of the atrial electrogram—delta

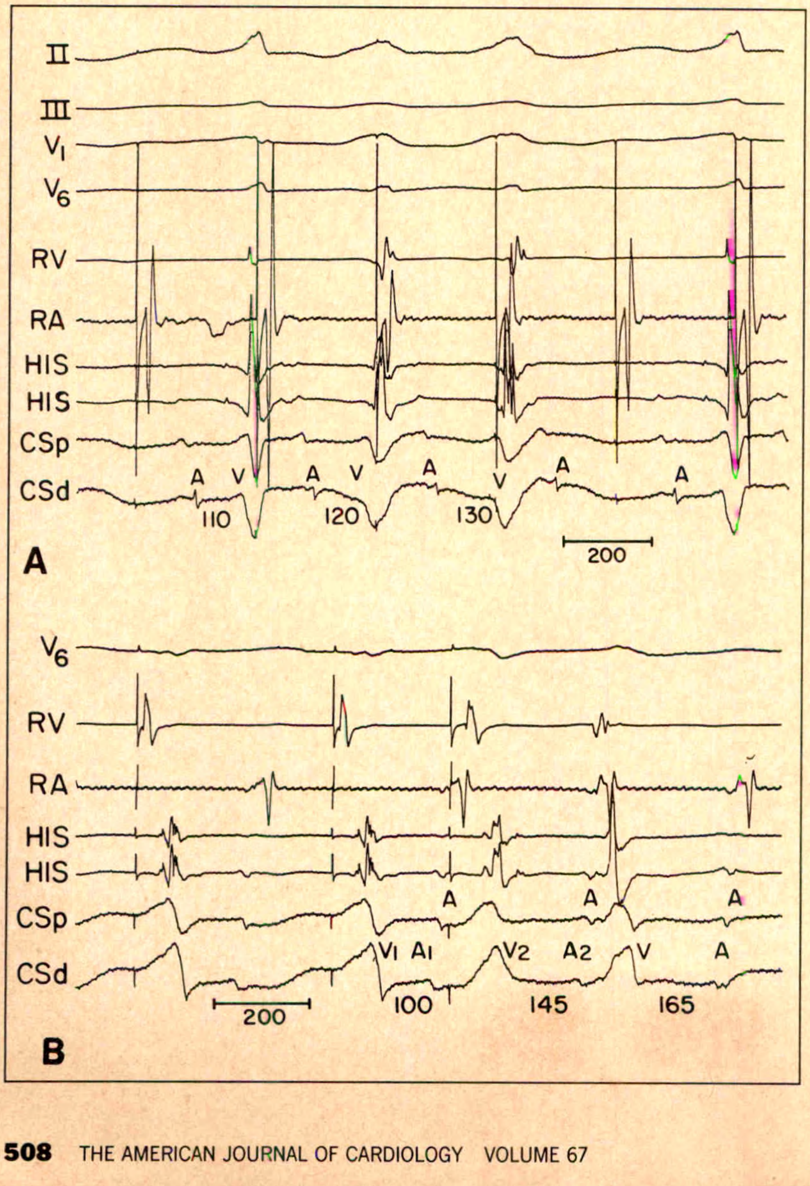

FIGURE 2. Electrophysiologic recordings from a patient with a left parietal accessory pathway. A = atrial electrogram; V = ventricular electrogram. *A,* right atrial (RA) straight pacing at cycle length of 280 ms. Note that the patient has progressive prolongation of the atrioventricular interval followed by a nonconducted atrial impulse. Preexcitation persists indicating that the Wenckebach block is occurring in the accessory pathway. *B,* right ventricular (RV) extrastimulus testing shows prolongation of the ventriculoatrial interval with the extrastimulus. The same eccentric retrograde activation sequence is maintained indicating that the decrement is occurring over the accessory pathway. Further decrement in the ventriculoatrial interval occurs with the repetitive ventricular response that follows the extrastimulus. Four surface leads (II,III,V_1,V_6), right ventricular, right atrial, His bundle (His), proximal coronary sinus (CSp) and distal coronary sinus (CSd) recordings are shown. A = atrial electrogram; V = ventricular electrogram.

wave interval—was 72.5 ± 38 ms. Anterograde accessory pathway conduction curves were continuous in all cases. The locations of anterograde decremental pathways were significantly different from the locations of the accessory pathways in the control population ($p < 0.001$) (Table II). Anterograde decremental conduction occurred almost entirely in right-sided and septal pathways.

Functional significance of anterograde decremental conduction: The 15 patients with anterograde decremental conduction were compared with the 131 patients with anterograde-conducting accessory pathways in the control group. The shortest RR interval between 2 preexcited QRS complexes in atrial fibrillation in patients with anterograde decremental accessory pathways was 288 ± 44 ms compared with 251 ± 65 ms in the control group ($p = 0.04$). The shortest RR interval was between 200 and 250 ms in 3 of the 15 patients with anterograde decremental pathways and >250 ms in the remaining 12 patients.

Retrograde decremental conduction: The shortest cycle length maintaining 1:1 retrograde conduction over the accessory pathway was 292 ± 52 ms and the retrograde accessory pathway effective refractory period was 268 ± 37 ms. Anterograde conduction over the accessory pathway was absent in 8 patients and preexcitation was intermittent in 3 patients. In the remaining patients, the shortest cycle length maintaining 1:1 anterograde conduction over the accessory pathway was 263 ± 61 ms and the accessory pathway effective refractory period was 273 ± 28 ms. Differences in anterograde and retrograde conduction were not significant. The maximal prolongation of the ventriculoatrial interval was 44.0 ± 30 ms. The degree of retrograde decremental conduction was thus less than the anterograde decremental conduction ($p < 0.05$). Again, retrograde accessory pathway conduction curves during ventricular extrastimulus testing were continuous in all cases. The locations of retrograde decremental pathways was similar to the locations of accessory pathways in the control group ($p = 0.98$).

Decremental conduction in both anterograde and retrograde directions: In patients with both anterograde and retrograde decrement ($n = 5$), the shortest cycle length maintaining 1:1 anterograde conduction over the accessory pathway was 290 ± 27 ms and the anterograde accessory pathway effective refractory period was 285 ± 20 ms. The shortest cycle length maintaining 1:1 retrograde conduction over the accessory pathway was 275 ± 34 ms and the retrograde accessory pathway effective refractory period was 260 ± 28 ms. One patient had anterograde and retrograde decrements over a left parietal accessory pathway. This was the only patient in whom the anterograde decrement could be demonstrated over a left parietal accessory pathway (Figure 2).

TABLE I Electrophysiologic Characteristics in Patients with Decremental Conduction

	Anterograde Conduction	Retrograde Conduction
Anterograde decrement		
Conduction over AP (no. of pts.)	15	6
SCL 1:1 (ms)	314 ± 54	285 ± 43
APERP (ms)	278 ± 42	259 ± 28
Decrement (ms)	72 ± 38	—
Retrograde decrement		
Conduction over AP (no. of pts.)	29	40
SCL 1:1 (ms)	268 ± 58	290 ± 51*
APERP (ms)	276 ± 28	267 ± 36
Decrement (ms)	44 ± 30	—

* $p = 0.09$.
AP = accessory pathway; APERP = accessory pathway effective refractory period; SCL 1:1 = shortest paced cycle length maintaining 1:1 conduction over the accessory pathway.

TABLE II Accessory Pathway Location

	Retrograde Decrement (n = 40)*	Anterograde Decrement (n = 15) (%)	Control (n = 171)†
Left parietal	19 (48)	1 (7)	86 (50)
Posterioseptal	13 (33)	4 (27)	55 (32)
Right parietal	2 (5)	7 (47)	10 (6)
Right anteroseptal	6 (15)	3 (20)	20 (12)
		$p < 0.001$	

* Five patients had both anterograde and retrograde decrements.
† Eight patients had 2 accessory pathways.

DISCUSSION

Decremental conduction occurring over accessory pathways has been reported infrequently.[4-10] The prevalence of this phenomenon in our large series of patients was 7.6%, confirming that its occurrence is uncommon. Decremental conduction over an accessory pathway has typically been associated with the presence of a nodoventricular fiber,[12-14] the permanent form of junctional reciprocating tachycardia[4-6] and as an electrophysiologic phenomenon discovered incidentally at electrophysiologic study.[7-9] In this study, a clinical pattern consistent with a nodoventricular fiber was present in 9 patients (18%). Four of these patients have undergone ablative surgery, at which time the pathways were demonstrated to be right parietal accessory pathways and not nodoventricular pathways in all cases. The permanent form of junctional reciprocating tachycardia was present in 6 patients (12%) and decremental conduction over the accessory pathway was an incidental finding at electrophysiologic study in the remaining 35 patients (70%).

Decremental conduction rarely occurred in both the anterograde and retrograde directions within the same pathway. Where decremental conduction was present in 1 direction, conduction was often absent in the other. These findings suggest that conduction over the accessory pathway in anterograde and retrograde directions is functionally distinct. Where conduction was bidirectional, there was a slight tendency for the shortest cycle length maintaining 1:1 conduction over the accessory pathway to be shorter in the direction in which decrement was absent.

Rate-independent conduction over accessory pathways may lead to rapid ventricular rates during atrial

fibrillation. Patients with anterograde decremental accessory pathways did have slower ventricular rates in atrial fibrillation than the control group with nondecremental accessory pathways. Despite this difference between the groups, 3 patients with decremental conduction had a shortest RR interval of <250 ms, indicating that decremental conduction did not protect all patients from potentially dangerous ventricular rates during atrial fibrillation.

The explanation for the occurrence of decrement over an accessory pathway is not known. In previously reported cases, the pathway has been located in close proximity to the atrioventricular node, raising the possibility that the pathway is an atrioventricular node-like structure.[5–10] In reported pathologic studies of patients with decrementally conducting accessory pathways, atrioventricular node-like cells have been identified in some cases.[15] These are invariably cases with septal or right parietal accessory pathways. Septal pathways were present in 22 of the patients (44%) in this study. Decremental conduction over the accessory pathway in 1 direction but not the other may be due to accessory pathway geometry or accessory pathway fiber orientation. Special catheter techniques to record accessory pathway potentials and more accurately define pathway location have led to the suggestion that many accessory pathways run an oblique course.[16] Pathologic examination of a septal accessory pathway in a patient who had the permanent form of junctional reciprocating tachycardia has been reported.[17] In this case, the accessory pathway took a serpiginous course, providing further support that accessory pathway geometry may contribute to decremental conduction. A role for impedance mismatch between the accessory pathway and the atrium or ventricle has also been suggested.[10,18]

The site of decrement could not be definitely determined with the methods used in this study. Conduction delay could have potentially occurred in the atrial or ventricular myocardium between the accessory pathway and recording electrodes. By measuring intervals at sites close to the origin and insertion of the accessory pathway, the likelihood that the decrement occurred in the atrium or ventricle and not over the accessory pathways was minimized. Support for decremental conduction occurring at the site of an accessory pathway, as demonstrated by recording accessory pathway potentials, has been provided previously.[10]

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Usefulness of d, l Sotalol for Suppression of Chronic Ventricular Arrhythmias

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Sotalol is a unique β-blocking drug, possessing significant class III antiarrhythmic activity. The efficacy and safety of 2 doses of sotalol (320 and 640 mg/day, divided in 2 doses) were compared to placebo in a 6-week randomized, double-blind, multicenter study of 114 patients with chronic ventricular premature complexes (VPCs) at frequencies of ≥30/hour. Sotalol significantly reduced VPCs in patients receiving both low (n = 38) and high (n = 39) doses, compared with patients (n = 37) receiving placebo (by 75 and 88%, respectively, vs 10%; p <0.001, sotalol vs placebo; p <0.05, high vs low dose). The individual efficacy criterion (≥75% VPC reduction) was achieved in 34% of low-dose and 71% of high-dose sotalol versus 6% of placebo-treated patients (p <0.003, sotalol vs placebo; p = 0.007, high vs low dose). Repetitive beats were suppressed 25% by placebo (difference not significant), 80% by low-dose (p <0.003) and 78% by high-dose sotalol (p <0.005). Sotalol decreased heart rate (by 24 to 25%, p <0.001) and increased PR (by 4 to 6%, p <0.001) and corrected JT intervals (by 12 to 13%, p <0.001), but did not change ejection fraction. Proarrhythmia (nonfatal) occurred in 3 sotalol and in 2 placebo patients. Nine discontinued therapy because of adverse effects (1 low dose and 8 high dose, p <0.02). In summary, sotalol is an efficacious antiarrhythmic drug for VPC suppression; in lower doses, it is somewhat less effective but better tolerated.

(Am J Cardiol 1991;67:511–516)

From the Department of Medicine, Division of Cardiology, University of Utah & LDS Hospital, Salt Lake City, Utah. This study was supported in part by grants from Bristol-Myers Company, Evansville, Indiana. Manuscript received July 30, 1990; revised manuscript received October 25, 1990, and accepted October 26.

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Beta-blocking drugs increase ventricular fibrillation threshold experimentally[1–3] and reduce rates of both sudden and total cardiac death in survivors of myocardial infarction.[4–6] Sotalol is a nonselective β-adrenergic receptor antagonist without sympathomimetic or membrane-stabilizing activity that also possesses class III antiarrhythmic activity.[7–9] It lengthens cardiac action potential without affecting conduction and increases canine ventricular fibrillation threshold. Sotalol, administered both orally and intravenously,[7–10] has been reported to be effective in the conversion of supraventricular arrhythmias,[11,12] and to act against ventricular arrhythmias.[13–16] Importantly, sotalol is reported to be effective for sustained or life-threatening ventricular arrhythmias,[17–21] and shows modest success for secondary prevention after myocardial infarction.[22] However, well-controlled trials are still needed to quantify the degree of sotalol's ventricular antiarrhythmic effects and to assess safety and tolerance. The present study was conducted to fulfill this need. An interim report consisting of an analysis of the first one-half of the study patients was previously presented.[13]

METHODS

Patient selection: Patients aged ≥18 years, with ≥30 ventricular premature complexes (VPCs) per hour on a 48-hour baseline electrocardiographic recording, for whom therapy was recommended (for reduction of symptoms or perceived mortality risk) were candidates for the study. Patients were excluded for advanced heart failure (functional class IV, ejection fraction ≤30%, lack of response to diuretics or digoxin, or cardiothoracic ratio ≥0.65), asthma, chronic pulmonary disease requiring medication, prior adverse reactions to β blockers, serum creatinine ≥3 mg/dl, uncontrolled systemic hypertension (diastolic pressure ≥120 mm Hg), unstable angina, myocardial infarction within 3 months and infective endocarditis.

Rhythm exclusions were heart rate at rest averaging ≤50 beats/min, sinus pauses ≥2.5 seconds, second- or third-degree atrioventricular block, sick sinus syndrome, bundle branch block, significant supraventricular arrhythmia, digitalis intoxication arrhythmia, corrected QT interval ≥0.45 second or PR interval ≥0.24 second, rhythm requiring pacemaker or emergency therapy, sustained ventricular tachycardia (>30 seconds, >120 beats/min) and primary ventricular fibrillation.

Concurrent antiarrhythmic medications, β blockers and drugs prolonging the QT interval (e.g., tricyclic

TABLE I Patient Characteristics at Entry

Study group	No. of Patients	Age (yr)	Sex (M/F)	Cardiac Diagnosis (%) CAD	SH	VHD	I	LVEF (%)
Placebo	37	58 ± 14	24/13	37	35	16	19	53 ± 9
Sotalol								
Low dose (320 mg/day)	38	57 ± 14	27/11	36	39	11	11	51 ± 10
High dose (640 mg/day)	39	61 ± 13	28/11	38	56	15	5	55 ± 10

CAD = coronary artery disease; I = idiopathic; LVEF = left ventricular ejection fraction; SH = systemic hypertension; VHD = valvular heart disease.
Mean values are ± standard deviation.

antidepressants) were not allowed. Institutional approval and informed consent were required before study entry.

Study design: The study was designed as a 6-week parallel, double-blind, randomized, placebo-controlled trial, comparing 2 doses of sotalol with placebo in suppression of chronic VPCs.

WEEK ONE: SCREENING BASELINE PHASE: Previous antiarrhythmic drugs were discontinued for ≥4 half-lives. Arrhythmia screening consisted of 2 consecutive 24-hour ambulatory recordings (≥18 analyzable hours in each). Recordings were analyzed blindly by Cardio Data Systems (Haddonfield, New Jersey). Medical history, physical examination, 12-lead electrocardiogram, chest x-ray, 20-channel blood chemistry testing, complete blood count and urinalysis were performed. Resting left ventricular ejection fraction was measured with equilibrium-gated radionuclide ventriculography.

WEEK TWO: SINGLE-BLIND, PLACEBO-BASELINE PHASE: One placebo tablet was given every 12 hours and a 48-hour ambulatory recording was obtained sometime between the third and seventh days. Interval history, cardiovascular examination and electrocardiogram were obtained.

WEEKS THREE TO SIX: DOUBLE-BLIND ACTIVE TREATMENT PERIOD: Patients were randomized to receive 160 or 320 mg of sotalol or placebo twice daily. Early ("first pass") treatment effects were determined by a 24-hour ambulatory recording obtained on day 2 after initiation of sotalol (week 3). Final efficacy assessment was made in week 6 by a 48-hour ambulatory recording. Laboratory tests, electrocardiography and radionuclide ventriculography were repeated.

Definition of efficacy: Effective suppression was defined as ≥75% reduction in total VPCs/hour or ≥90% reduction in repetitive VPCs/hour or ventricular tachycardia events per day on the final (6-week) recording, or all, compared with the 48-hour placebo-baseline recording.

Statistical methods: Because arrhythmia frequencies were not normally distributed, responses were compared statistically after logarithmic transformations [ln(VPCs/hour + 0.25)]. Analysis of variance was performed for repeated measures (i.e., at screening baseline, placebo-baseline and early and final treatment phases) for each group (placebo and sotalol, low and high doses). Pairwise comparisons were then made between time phases within groups by Wilcoxon's test for nonparametric analysis. Comparisons of arrhythmia response (defined for individual patients by the ratios of frequencies during final or early treatment and placebo-baseline phases) were made among the 3 groups with the Cochran-Mantel-Hanszel analysis. Student's paired *t* test was used to assess changes in electrocardiographic intervals, heart rate and blood pressure during therapy. The Fisher exact text was used to test for differences in the incidence of on-treatment conditions among the 3 groups. Average percent suppression for a treatment group was obtained by averaging the individual patient values in that group for simple percent suppression. A p value ≤0.05 (2-tailed hypothesis) was considered statistically significant.

RESULTS

Comparison of baseline characteristics: A total of 178 patients underwent ambulatory monitoring screening. Of these, 126 qualified and entered the single-blind placebo-baseline phase. Criteria for randomization were met in 114, who entered the double-blind treatment phase. Baseline characteristics of patients in the placebo and the 2 sotalol groups were similar (Table I). The mean frequency of total and repetitive VPCs did not differ among groups (343 vs 382/hour vs 352 and 5.3/hour vs 7.2 vs 8.5/hour, respectively, Table II). Left ventricular ejection fraction was also similar (53 vs 51 vs 55%). Of the 114 patients, 12 were excluded from the primary efficacy analysis—9 for protocol violations (3 in each group) and 3 for miscellaneous reasons (1 bradycardia and syncope, 1 bradycardia, and 1 death from myocardial infarction). Thus, 102 patients could be assessed for efficacy, 96 for the initial period and 92 for the final efficacy period. All 114 patients entering double-blind treatment were assessed for safety.

Results for final treatment phase: TOTAL VENTRICULAR PREMATURE COMPLEXES PER HOUR: A successful result was obtained at the 6-week end point for suppression of total VPCs for low-dose ($p < 0.001$) and high-dose ($p < 0.001$) sotalol-treated patients but not for placebo-treated patients ($p = 0.77$). Total VPCs/hour were reduced only 10% by placebo (from 343/hour at placebo-baseline to 315/hour at final Holter recording), 75% by 160 mg of sotalol per day (320 mg/day, from 382 to 94/hour) and 88% by 320 mg of sotalol twice per day (640 mg/day, from 352 to 38/hour) (Figure 1, Table

TABLE II Group Response of Ventricular Arrhythmias

Treatment Group (n)	Placebo-Baseline TVPCs/RVPCs/VT Log. Mean Frequency [95% CL]	Early Treatment TVPCs/RVPCs/VT Log. Mean Frequency (% Suppression vs Placebo-Baseline)* [95% CL]	Final Treatment TVPCs/RVPCs/VT Log. Mean Frequency (% Suppression vs Placebo-Baseline)* [95% CL]
Placebo (32)	343 / 5.3 / 10.3 [248, 474] [2.4, 11.5] [3.7, 28.3]	310 (6) / 4.5 (9) / 5.2 (25) [211, 455] [1.8, 10.6] [1.4, 18.3]	315 (10) / 4.2 (25) / 6.0 (41) [211, 468] [1.4, 8.8] [2.3, 15.2]
Sotalol 320 mg/day (32)	382 / 7.2 / 21.5 [278, 525] [2.9, 17.1] [7.7, 59.5]	80 (79) / 2.2 (69) / 1.9 (92) [32, 199] [0.8, 5.4] [0.6, 5.3]	94 (75) / 1.5 (80) / 2.0 (91) [50, 177] [0.5, 3.4] [0.5, 6.4]
Sotalol 640 mg/day (28)	352 / 8.5 / 11.4 [246, 506] [4.7, 15.2] [5.7, 22.7]	54 (85) / 1.2 (83) / 0.8 (90) [26, 112] [0.5, 2.4] [0.3, 1.8]	38 (88) / 1.4 (78) / 1.8 (82) [17, 82] [0.6, 3.1] [0.6, 5.2]

* Percent average suppression obtained by averaging values for individual percent suppression.
CL = confidence limits; Log. = logarithmic; RVPCs = repetitive ventricular premature complexes per hour; TVPCs = total ventricular premature complexes per hour; VT = unsustained ventricular tachycardia events.
TVPCs and RVPCs are given per hour; VT events are given per day.

II). The percent reduction of total VPCs per hour achieved by either dose of sotalol differed significantly from placebo ($p < 0.005$, for both comparisons). Suppression was also significantly greater with 640 mg of sotalol per day than with 320 mg of sotalol per day ($p < 0.05$).

Individual efficacy (≥75% VPC suppression) was achieved in 6% of placebo patients (2 patients), 34% of low-dose sotalol (n = 11, $p < 0.003$ vs placebo), and 71% of high-dose sotalol patients (n = 20, $p < 0.001$ vs placebo, p = 0.007 vs low dose) (Figure 2, Table III).

REPETITIVE VENTRICULAR PREMATURE COMPLEXES: Significant differences between placebo and sotalol were also evident for reductions in repetitive VPCs per hour and ventricular tachycardia events per day. Repetitive VPCs were reduced only 25% by placebo, 80% by low-dose sotalol ($p < 0.003$) and 78% by high-dose sotalol ($p < 0.005$) (Figure 1, Table II).

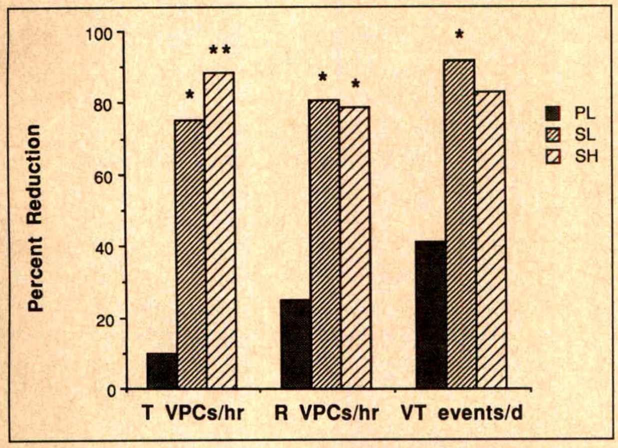

FIGURE 1. Comparative responses of total ventricular premature complexes (T VPCs) and repetitive VPCs (R VPCs) per hour and ventricular tachycardia (VT) events per day to sotalol and placebo. *Left column,* percent reduction in average hourly T VPCs in placebo (PL), low-dose sotalol (SL) and high-dose sotalol (SH) groups. *Middle and right columns,* percent reduction in average hourly R VPCs and daily VT events, respectively, in the same groups. * p <0.05 vs PL; ** p <0.05 vs SL and PL.

Individual efficacy (≥90% suppression of repetitive VPCs) was achieved in 18% of placebo patients (n = 5), 52% of low-dose (n = 14, $p < 0.01$ vs placebo) and 44% of high-dose sotalol patients (n = 12, $p < 0.05$ vs placebo) (Figure 2, Table III).

Suppression of daily ventricular tachycardia events generally paralleled the response for repetitive VPCs (Figures 1 and 2, Tables II and III).

Results for early treatment phase: The early efficacy of treatment was assessed between days 2 and 3 of double-blind therapy. Total VPCs were reduced by 6% early during therapy by placebo (difference not significant), 79% by low-dose sotalol ($p < 0.001$) and 85% by high-dose sotalol ($p < 0.001$, Table II). Thus, the efficacy of sotalol was virtually completely achieved within the first 2 to 3 days of dosing.

Early suppression of repetitive VPCs per hour averaged 9% with placebo (difference not significant), 69% with low-dose (p = 0.004) and 83% with high-dose sotalol ($p < 0.001$). Ventricular tachycardia events were re-

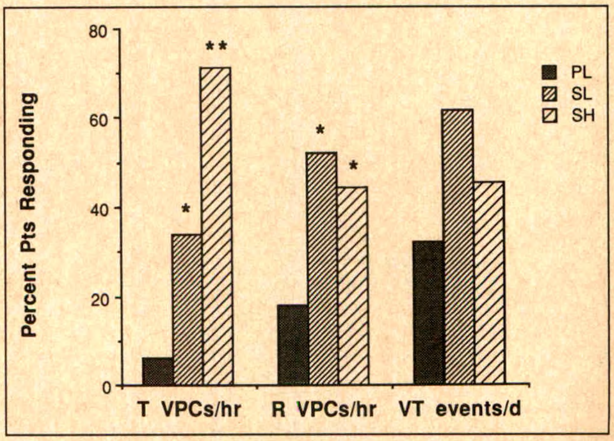

FIGURE 2. Percentage of patients, *left column,* achieving ≥75% reduction in total ventricular premature complexes (T VPCs); *middle column,* ≥90% reduction in repetitive VPCs (R VPCs); and, *right column,* in ventricular tachycardia (VT) events in placebo (PL), low-dose sotalol (SL) and high-dose sotalol (SH) groups (comparing placebo-baseline and 6-week recordings). * p <0.05 vs PL; ** p <0.05 vs SL and PL.

TABLE III Percentage of Patients Reaching Target Suppression* at Final Assessment

Treatment Group (no. of pts.)	Total VPCs/Hour % (n)	Repetitive VPCs/Hour % (n)	VT Events/Day % (n)
Placebo (32)	6 (2/32)	18 (5/28)	32 (6/19)
Sotalol 320 mg/day (32)	34† (11/32)	52† (14/27)	61 (11/18)
Sotalol 620 mg/day (28)	71‡ (20/28)	44 (12/27)	45 (9/20)

* ≥75% suppression in total VPCs/hour or ≥90% suppression in repetitive VPCs/hour or VT events/day.
† p <0.05 vs placebo.
‡ p <0.05 vs placebo and sotalol 320 mg/day.
VPCs = ventricular premature complexes; VT = ventricular tachycardia (≥3 successive VPCs, ≥120 beats/min).

duced by 44% (difference not significant), 92% (p = 0.001) and 90% (p = 0.001), respectively.

Diurnal effects on arrhythmia: A diurnal variation in the average hourly VPC frequency was observed in both the placebo and sotalol study groups at baseline (Figure 3), with rates increasing during waking hours (6 A.M. to midnight), peaking between 2 and 3 P.M., then decreasing during evening and nighttime hours and reaching a nadir between 4 and 5 A.M. This diurnal pattern was unaffected by placebo therapy but virtually abolished by sotalol.

Electrocardiographic and ejection fraction responses (Table IV): Heart rate decreased by an average of 19 beats/min (−25%) during low-dose and by 16 beats/min (−24%) during high-dose sotalol therapy (p <0.001 for each) but was unchanged during placebo. PR interval increased slightly (+6%) but significantly (p <0.001) with both doses of sotalol. QRS duration did not change. QT interval increased by an average of 80 ms (+21%) during low-dose (p <0.001 vs baseline) and

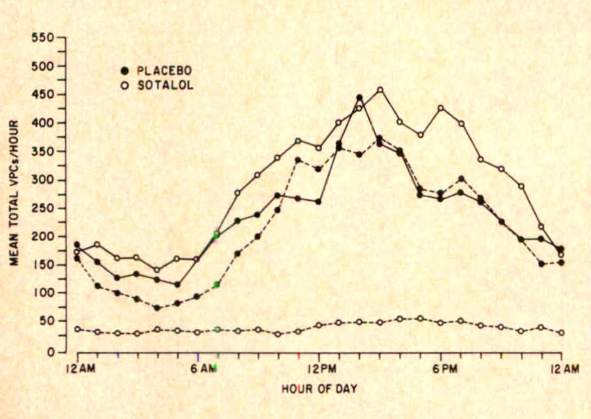

FIGURE 3. Effects of sotalol (combined treatment groups; *open circles*) versus placebo *(closed circles)* on diurnal frequency of total ventricular premature complexes (VPCs). Baseline frequencies for the 2 groups are represented by *solid lines* and treatment frequencies (6-week end point) by *dashed lines*. Total VPC frequency is expressed as the logarithmic mean per hour, by the hour of day. Differences are only significant for the sotalol treatment curve, compared with each of the other 3 curves.

TABLE IV Electrocardiographic and Ventriculographic Changes

Variable	Treatment Group	Placebo-Baseline	Final*	p Value
PR (ms)	Placebo	178 ± 33	176 ± 31	NS
	320 mg	168 ± 39	175 ± 40	<0.001
	640 mg	179 ± 34	189 ± 30	<0.001
QRS (ms)	Placebo	90 ± 15	90 ± 20	NS
	320 mg	92 ± 23	89 ± 21	NS
	640 mg	90 ± 15	92 ± 11	NS
QT (ms)	Placebo	375 ± 38	388 ± 38	0.002
	320 mg	377 ± 36	457 ± 50	<0.001
	640 mg	393 ± 37	484 ± 47	<0.001
QTc (ms)	Placebo	414 ± 26	424 ± 29	0.02
	320 mg	418 ± 34	439 ± 36	0.008
	640 mg	413 ± 36	443 ± 44	0.002
JT (ms)	Placebo	284 ± 38	297 ± 36	0.002
	320 mg	285 ± 31	368 ± 52	<0.001
	640 mg	303 ± 37	392 ± 47	<0.001
JTc (ms)	Placebo	314 ± 29	325 ± 33	0.01
	320 mg	316 ± 27	354 ± 40	<0.001
	640 mg	318 ± 32	359 ± 42	<0.001
Heart rate (beats/min)	Placebo	75 ± 12	73 ± 13	NS
	320 mg	75 ± 12	56 ± 8	<0.001
	640 mg	67 ± 12	51 ± 7	<0.001
LVEF (%)	Placebo	53 ± 9	52 ± 9	NS
	320 mg	51 ± 10	54 ± 9	0.01
	640 mg	55 ± 10	59 ± 10	0.008

* Days 19 to 39.
Values are mean ± standard deviation.
320 mg = 320 mg/day of sotalol, divided into 2 doses; 640 mg = 640 mg/day of sotalol divided into 2 doses.
LVEF = left ventricular ejection fraction; NS = difference not significant.

91 ms (+23%) during high-dose sotalol (p <0.001 vs baseline). The corrected QT interval showed more modest increases, averaging 21 ms (+5%) during low-dose (p = 0.008) and 30 ms (+7%) during high-dose therapy (p = 0.002). Changes in JT and corrected JT intervals paralleled changes in QT and corrected QT intervals. Interestingly, minor increases in QT, corrected QT, JT and corrected JT intervals were also observed with placebo. High-dose sotalol led to greater prolongation than low-dose sotalol for all intervals, but none of the interdose comparisons was significant.

Left ventricular ejection fraction was not adversely affected by sotalol. In fact, ejection fraction increased at the late therapy assessment with both high-dose (0.55 to 0.59, p = 0.008) and low-dose sotalol (0.51 to 0.54, p = 0.01), but did not change with placebo (0.53 to 0.52).

Adverse effects: Adverse effects were reported frequently in all 3 groups (43 to 72% incidence) but tended to be most frequent in the high-dose sotalol group. Adverse effects were considered to be related to treatment by the blinded investigators in 11% of placebo, 39% of low-dose and 51% of high-dose sotalol patients. Three patients (8%) receiving low-dose and 8 (21%) receiving high-dose sotalol reported dyspnea. Bradycardia occurred in 4 (11%) low-dose and 5 (13%) high-dose sotalol patients, and fatigue in 8 patients (21%) in each sotalol group.

Discontinuation of sotalol was required in 9 patients: 1 (3%) receiving low-dose sotalol, because of fatigue, and 8 (21%) receiving high-dose sotalol (p <0.02, high

vs low dose), because of symptomatic bradycardia in 4 (1 patient also had syncope and nonsustained polymorphic ventricular tachycardia), fatigue in 2, heart failure in 1 and dizziness in 1.

Proarrhythmia (based on investigator judgment) was observed in 2 patients taking placebo (1 each with increased VPCs and events of ventricular tachycardia), 1 patient taking low-dose sotalol (increased VPCs only), and 2 taking high-dose sotalol (1 with increased events of ventricular tachycardia and new sustained ventricular tachycardia, and 1 with syncope, bradycardia and nonsustained polymorphic ventricular tachycardia).

One patient died 20 hours after ingesting an estimated 2 doses (320 mg) of sotalol. Severe chest pain occurred 4 hours before randomization; death is believed to be from myocardial infarction.

Laboratory abnormalities, observed in 5 placebo, 2 low-dose and 3 high-dose sotalol patients, were not considered to be treatment-related.

DISCUSSION

Study summary: This multicenter, placebo-controlled study clearly demonstrates that sotalol is effective in reducing the frequency of total VPCs, repetitive VPCs and events of ventricular tachycardia in patients with chronic complex ventricular arrhythmias. Response was dose-dependent for total VPCs (88% suppression for high-dose and 75% for low-dose sotalol) but not for repetitive VPCs (78% suppression for high dose and 80% for low dose). Antiarrhythmic effect was well established by day 2 to 3 (early study) and persisted over 3 weeks (late study). Tolerability was better with the low dose than with the high dose. The expected electrocardiographic changes occurred, but depression of left ventricular function was not observed.

Efficacy potential for ventricular tachyarrhythmias: In addition to its efficacy in suppressing VPCs,[13-15] sotalol may represent an important addition to therapy for life-threatening ventricular tachyarrhythmias.[17-21] Sotalol increases the ventricular fibrillation threshold in experimental animals and causes favorable trends in mortality after myocardial infarction in humans.[22] In an important early clinical study, 45 of 50 patients with recurrent, sustained ventricular tachycardia or fibrillation underwent electrophysiologic testing before and after receiving sotalol.[18] The arrhythmia became noninducible in 10, was slower and well tolerated in 12, and remained poorly tolerated in 23. Ten patients with noninducible and 11 with stable ventricular tachycardia were treated with oral sotalol. No recurrence was observed in the noninducible group, whereas 37% in the inducible group had subsequent ventricular tachycardia or sudden death. In another study,[19] 12 of 14 patients receiving sotalol remained clinically free of sustained ventricular tachycardia after a mean of 19 ± 7 months. Ruder et al[21] reported on 65 patients with refractory sustained ventricular tachycardia or fibrillation treated with oral sotalol. Efficacy was evaluated in 54 after 11.5 ± 6 months. Actuarial success was 54 ± 13% at 6 months and 47 ± 13% at 12 months.

Electrocardiographic effects of sotalol: The electrocardiographic effects of sotalol observed in our study were those expected from its known pharmacologic actions and are similar to those observed by others.[7-11] These consisted of modest to moderate lengthening of the sinus cycle and PR, corrected QT and corrected JT intervals. Sotalol also lengthens cardiac refractory periods, a class III antiarrhythmic effect.[7-10]

Adverse potential: Adverse effects typical of β blockade (such as fatigue and bradycardia) were noticed with variable, dose-related frequency in this study, as in previous ones.[13,18,21] Discontinuation was required in only 1 patient (3%) in the low-dose group, but in 8 (21%) in the high-dose group. In addition, sotalol is known to possess proarrhythmic potential. Specifically, torsades de pointes (polymorphic ventricular tachycardia associated with a prolonged QT interval) has been reported with sotalol, although infrequently (1.1% of patients treated for nonsustained ventricular tachycardia or VPCs, or both, in the data base of Bristol-Myers Company, October 17, 1990). In our study, a small risk of proarrhythmia was observed. Nonfatal proarrhythmic ventricular tachycardia events occurred in 2 patients in the high-dose group. Ruder et al[21] reported exacerbation of ventricular arrhythmia in 9% of patients in a more diseased population. These rates are acceptably low compared with those of other antiarrhythmic drugs but warrant further assessment.

Study limitations: Patients included in the present study had complex ventricular arrhythmias but were clinically stable, and did not have sustained ventricular tachycardia or fibrillation. Other unstable patients, such as those with recent myocardial infarction, were also excluded, and left ventricular ejection fraction averaged >50%. Thus, caution should be applied in relating our results to patients with more serious arrhythmias or more depressed function. Proarrhythmia was infrequent in this study, but its size is inadequate to define the risk of serious proarrhythmia precisely, including torsades de pointes. The ability of antiarrhythmic therapy to reduce the increased cardiac mortality associated with complex arrhythmias in patients with structural heart disease has not been demonstrated and the risk/benefit ratio must be established for each individual agent.[23]

Clinical implications: Our study clearly indicates that complex ventricular arrhythmias can be effectively controlled with sotalol over several weeks, associated with generally mild and dose-related adverse potential. Because of its β-blocking effects, sotalol may be particularly useful, and possibly preferred to class I antiarrhythmic drugs, for treatment of symptomatic arrhythmias occurring in the setting of chronic ischemic heart disease or increased sympathoadrenal stimulation, including patients with angina, hypertension and previous myocardial infarction. Sotalol has additional class III actions and provides greater antiarrhythmic activity than that expected from standard β blockers.[14,15,17-21] Whether sotalol, or any other antiarrhythmic drug, should be used prophylactically to reduce the risk associated with prognostically significant but asymptomatic

ventricular arrhythmias is uncertain and the risk/benefit ratio of such treatment will require specific assessment in larger mortality trials.[22,23]

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Doppler Echocardiographic Comparison of the Carpentier and Duran Anuloplasty Rings Versus No Ring After Mitral Valve Repair for Mitral Regurgitation

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To compare the hemodynamic results of different anuloplasty techniques of primary valve repair for mitral regurgitation, 122 patients were prospectively studied with Doppler echocardiograms 5 to 10 days after operation. Seventy-seven patients had mitral valve prolapse, 27 had coronary artery disease, 13 patients had rheumatic mitral valve lesions and 5 patients had infective endocarditis. Forty-eight patients received the flexible Duran ring, 46 received the more rigid Carpentier ring and 28 patients received no ring. Doppler echocardiography demonstrated a significant decrease in mitral valve area estimated by the pressure half-time method in patients who received either a Carpentier (2.6 ± 0.8 cm^2) or Duran ring (2.8 ± 0.8 cm^2) when compared with patients who received no ring (3.2 ± 0.7 cm^2) ($p = 0.01$). No significant differences were observed for peak transmitral diastolic velocity, peak transmitral diastolic gradient, or the grade of mitral regurgitation by color flow Doppler mapping between patients with and without rings. The etiology of mitral disease and concomitant surgical procedures accompanying mitral valve repair did not significantly influence mitral valve area, peak velocity or peak gradient. These data suggest that Carpentier and Duran rings decrease the hemodynamic mitral valve area; however, the decrease in valve area is small and not associated with a clinically important increase in transvalvular gradient.

(Am J Cardiol 1991;67:517–519)

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Mitral valve repair to correct mitral valve regurgitation has been in use for >30 years.[1–3] Successful mitral valve repair results in lower operative mortality, late mortality, reoperation rates and valve-related complications compared with mitral valve replacement.[4,5] Mitral valve repair may decrease the frequency of postoperative low-output syndrome because it preserves the natural geometry of the left ventricle by maintaining papillary muscle integrity.[6,7] In addition, long-term studies have indicated that mitral valve repair may be more durable than bioprosthetic replacement.[8,9] Several different techniques of mitral valve repair have been used. Carpentier et al[10] modified mitral valve repair by the insertion of a semiflexible ring; a more flexible ring was developed by Duran et al.[11] This study compares early postoperative hemodynamic results of mitral valve repair with either the Carpentier or Duran ring versus repair with no ring.

METHODS

Between January 1984 and September 1989, 166 patients with pure mitral regurgitation were treated with mitral valve repair at Brigham and Women's Hospital. Of these patients, 122 (81 men and 41 women, mean age ± standard deviation 62 ± 13 years) were randomly selected to receive postoperative Doppler echocardiograms 5 to 10 days postoperatively. Seventy-seven patients had mitral valve prolapse, 27 patients had coronary artery disease, 13 patients had rheumatic mitral valve lesions and 5 patients had active infective endocarditis (Figure 1). Patients with hemodynamic evidence of preoperative mitral stenosis were excluded from the study.

Operative technique: The wide variety of pathology treated in this group necessitated a multitude of techniques including anterior and posterior leaflet resection, trench chordoplasty, the flip-over technique for chordal replacement, and 3 different forms of treatment to the anulus. The decision regarding the use of different rings or no ring depended on a variety of factors. The Carpentier ring was used earlier in our experience, but as we increased our experience with myxomatous mitral valve repair we have shown that the more flexible Duran ring appears to be preferable for these very enlarged anuli. The Carpentier ring often "telescopes" the large amount of tissue of the dilated floppy valve into

TABLE I Influence of Etiology on Early Postoperative Mitral Valve Function

Etiology	MVA (cm^2)	Peak V (m/s)	Gradient (mm Hg)
Myxomatous	2.8 ± 0.9	1.3 ± 0.3	7.0 ± 3.7
Ischemic	2.9 ± 0.7	1.3 ± 0.3	7.3 ± 2.7
Rheumatic	2.8 ± 0.8	1.5 ± 0.3	8.9 ± 3.5
Endocarditis	2.7 ± 1.0	1.2 ± 0.3	5.6 ± 3.2

No significant influence of etiology on Doppler parameters was detected.
Gradient = peak transmitral diastolic gradient; MVA = mitral valve area; Peak V = peak transmitral early diastolic velocity.

the left ventricular outflow tract and cause outflow obstruction. There were some patients in this series for whom it was decided that no ring would be important, particularly those who had infective endocarditis, where the absence of prosthetic material is a benefit in the presence of mitral regurgitation, or where tissue was extremely friable and the anulus was not dilated.

Echocardiographic evaluation: Two-dimensional echocardiograms were recorded in the left lateral decubitus position with a Hewlett-Packard 77020 AC/AR phased-array ultrasonoscope device using a 2.5-MHz transducer. Pulsed-wave Doppler sampling of transmitral flow was recorded from the apical 4-chamber view with the sample volume bisecting the mitral valve anulus (parallel to the direction of blood flow); after January 1987, these studies were supplemented by color Doppler flow mapping. The pressure half-time was calculated from the deceleration of the early diastolic flow signal; mitral valve area was estimated by[12]: mitral valve area (cm) = 220/pressure half-time in milliseconds. The peak transmitral early diastolic gradient was calculated from the peak diastolic flow velocity by the simplified Bernoulli equation.[13] Mitral regurgitation was semiquantitated on a scale of 0+ to 4+, as previously described, by a clinical echocardiographer unaware of details of operative technique.[14]

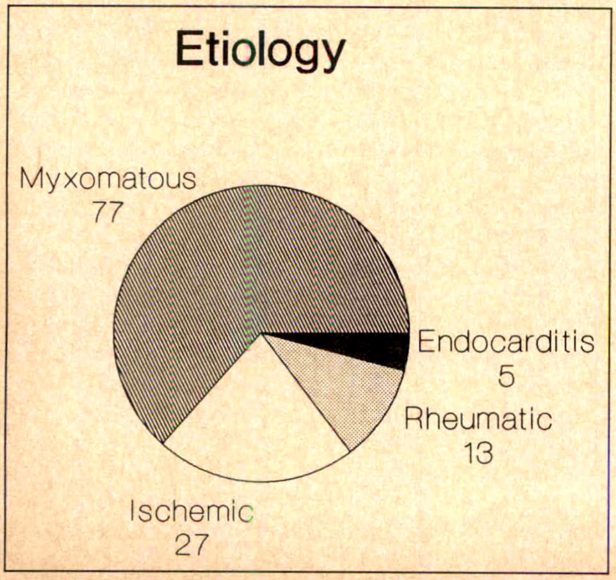

FIGURE 1. Distribution of pathology of 122 patients undergoing mitral valve repair.

TABLE II Influence of Repair Technique on Early Postoperative Mitral Valve Function

	MVA (cm^2)	Peak V (m/s)	Gradient (mm Hg)
No ring	3.2 ± 0.7	1.2 ± 0.4	6.5 ± 3.9
Carpentier ring	2.6 ± 0.8*	1.4 ± 0.3	8.0 ± 3.1
Duran ring	2.8 ± 0.9*	1.3 ± 0.3	6.9 ± 3.5

* Significantly different from no ring ($p < 0.05$).
Gradient = peak transmitral diastolic gradient; MVA = mitral valve area; Peak V = peak early transmitral diastolic velocity.

TABLE III Influence of Concomitant Surgical Procedures on Early Postoperative Mitral Valve Function

Procedure	MVA (cm^2)	Peak V (m/s)	Gradient (mm Hg)
None	2.9 ± 0.9	1.3 ± 0.3	6.9 ± 3.8
CABG	2.7 ± 0.7	1.4 ± 0.3	7.8 ± 3.1
Others	2.7 ± 0.5	1.2 ± 0.1	6.1 ± 1.2
	$p = 0.52$	$p = 0.26$	$p = 0.37$

CABG = coronary artery bypass graft surgery; Gradient = peak transmitral diastolic gradient; MVA = mitral valve area; Peak V = peak early transmitral diastolic velocity.

Statistical analysis: Doppler variables were compared with etiologies of valve disease and surgical technique by analysis of variance. Comparisons of Doppler variables were performed using both nonparametric and parametric tests; because results were nearly identical, results from Student's *t* tests are presented. Results are expressed as mean ± 1 standard deviation.

RESULTS

Influence of etiology of valve disease: Of the 122 patients studied, 112 (92%) had a postoperative mitral regurgitation grade of ≤2+/4+. Of the 77 patients with myxomatous mitral valve disease, 73 (95%) had postoperative mitral regurgitation grades of ≤2+. Twelve of 13 patients (92%) with rheumatic valve disease, 22 of 27 patients (81%) with coronary artery disease, and 5 of 5 (100%) of those with infective endocarditis also had mitral regurgitation grades of ≤2+/4+. There was no significant influence of etiology on the postoperative mitral valve area, peak transmitral velocity or peak transmitral gradient (Table I). Systolic anterior motion of the mitral valve was not observed in these patients.

Influence of repair technique: There was no significant difference in postoperative mitral regurgitation grades between patients who received Carpentier rings, Duran rings or no ring. However, the mitral valve area was significantly larger in patients who had mitral valve repairs without rings than in patients who had received either a Carpentier or a Duran ring ($p = 0.01$) (Table II). In contrast, no significant difference in mitral valve area was detectable between patients with Carpentier or Duran rings. There was a trend toward higher peak transmitral velocities and gradients among patients who received rings when compared with those without rings in whom statistical significance was not reached ($p = 0.09$).

Influence of concomitant procedures: No significant differences were observed between postoperative mitral

regurgitation grades of patients who underwent mitral valve repair with or without accompanying coronary bypass surgery or aortic valve replacement (p = 0.37). Seventy of the 75 patients (93%) with no additional surgical procedure, 40 of 45 patients (89%) with bypass surgery, and 2 of 3 with aortic valve replacement had postoperative mitral regurgitation grades of ≤2+. Postoperative mitral valve area, peak diastolic velocity and peak gradients did not differ significantly among these groups (Table III).

DISCUSSION

A variety of techniques have been advocated for surgical repair for mitral regurgitation. Recent studies suggest that the flexible Duran ring, which allows changes in shape during the cardiac cycle, may be more desirable. In addition, mitral valve repair may be performed without anuloplasty.[15] In this study, prospective Doppler echocardiography studies demonstrated that patients with rings had changes in transmitral flow indicating a smaller hemodynamic orifice size. Although this decrease in valve area was statistically significant, it is not clinically important, since no change in diastolic gradient was observed.

Because this study was not randomized and some patients did not receive echocardiograms, these results may have been influenced by selection bias. However, there is no reason to believe that patients with smaller mitral valves would be more likely to receive anuloplasty rings. In addition, this study predated the use of intraoperative transesophageal echocardiography in our institution. Because this technique can influence surgical technique and outcome,[16] it is possible that current observations would be different. Another potential limitation in this study is the use of the pressure half-time method of estimating mitral valve area. The pressure half-time is dependent on initial pressure gradient across the valve as well as atrioventricular compliance.[17,18] Because peak transmitral velocities were not significantly different between the patients who did and did not receive rings, it is unlikely that initial pressure gradients were different between the 2 groups; in addition, changes in atrioventricular compliance would most likely be apparent in both groups of patients.

Thus, although the decrease in mitral valve anulus size after ring repair was evident by Doppler echocardiography in this study, mitral valve gradients were not increased among patients with rings. These data support the use of anuloplasty rings in properly selected patients, depending on the valve pathology and anular dynamics.

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Influence of Sympathetic Stimulation and Parasympathetic Withdrawal on Doppler Echocardiographic Left Ventricular Diastolic Filling Velocities in Young Normal Subjects

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To determine the effects of parasympathetic withdrawal or sympathetic stimulation on Doppler echocardiographic measures of left ventricular diastolic filling, we studied 10 young normal subjects aged 21 to 29 years during separate infusions of atropine (0.8 mg followed by 0.4 mg every 10 minutes until heart rate >110 beats/min or a total dose of 2 mg was attained) and epinephrine (10, 25 and 50 ng/kg/min for 12 minutes each). At the highest atropine dose, heart rate increased from 60 ± 9 to 105 ± 8 beats/min (mean ± standard deviation), the diastolic filling period decreased by 61% (573 ± 141 to 222 ± 34 ms), the peak early (E) filling decreased 23% (77 ± 12 to 61 ± 11 cm/s), the peak atrial (A) filling increased 103% (40 ± 6 to 81 ± 17 cm/s), and the E/A ratio decreased by 60% (2.0 ± 0.5 to 0.8 ± 0.3) (all p <0.001). These alterations were not correlated to changes in systolic function, preload, blood pressure or plasma catecholamines, all of which were unchanged. However, atropine-induced changes in diastolic filling period were highly correlated to changes in E peak (r = 0.64, p <0.01), A peak (r = −0.95, p <0.001) and the E/A ratio (r = 0.93, p <0.001). The effects of atropine on the E/A ratio were normalized by dividing the E/A ratio by the diastolic filling period (E/A/diastolic filling period).

At the highest epinephrine dose, plasma epinephrine increased from 94 ± 59 to 879 ± 310 ng/liter, the heart rate increased by 26% (58 ± 8 to 73 ± 7 beats/min), the diastolic filling period decreased by 22% (596 ± 144 to 464 ± 127 ms), peak E increased 43%, peak A increased by 30% (40 ± 6 to 52 ± 9 cm/s) (all p <0.01), the E/A ratio increased 15% (2.0 ± 0.5 to 2.3 ± 0.6, p = 0.13), and the E/A/diastolic filling period increased by 43% (3.5 ± 0.6 to 5.0 ± 1.3, p <0.01). Increases in epinephrine levels directly correlated to increases in E peak (r = 0.74, p <0.001), A peak (r = 0.58, p <0.01) and the E/A/diastolic filling period (r = 0.59, p <0.01).

It is concluded that parasympathetic withdrawal reduces E and increases A filling velocities and reduces the E/A ratio. These changes are closely related to changes in diastolic filling period and heart rate. In contrast, epinephrine at physiological levels increases E, A and the E/A/diastolic filling period. These findings document the importance of controlling for these factors if Doppler filling velocities are used to study diastolic function.

(Am J Cardiol 1991;67:520–526)

Doppler echocardiography has been widely used to study left ventricular (LV) diastolic function. However, multiple factors including age, ischemic heart disease and prior myocardial infarction may have significant and contrasting effects on diastolic filling velocities.[1–2] In addition, changes in heart rate, which are mediated by both parasympathetic and sympathetic activity, have correlated with changes in diastolic measures in prior studies.[1–5] Cardiovascular adjustments to most stresses are mediated in part by the autonomic nervous system, with parasympathetic withdrawal and sympathetic activation typically occurring at the onset of stress.[6–8] Although the effects of both parasympathetic withdrawal and sympathetic stimulation on chronotropy and inotropy are relatively completely understood,[9–14] much less is known regarding their effects on LV filling.

There are only limited data, using dopamine or dobutamine infusions, on the effects of sympathetic stimulation on diastolic measurements.[12,13,15,16] Because the individual effects of differing factors affecting diastolic filling velocities may be obscured by their contrasting influences, we studied young, normal men to define the effects of parasympathetic withdrawal (using atropine) and sympathetic stimulation (using epinephrine). Although such an age limitation and subject selection may limit the general validity of the results, it minimizes the effects of age and other factors such as disease. Our results document significant effects of both parasympathetic withdrawal and sympathetic stimulation on dia-

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stolic filling velocities, which must be considered if Doppler echocardiography is used to study diastolic function.

METHODS

Subjects: Ten normal men aged 21 to 29 years (mean ± standard deviation 25 ± 2) were studied after an overnight fast. Before inclusion in the study, normal cardiovascular function was documented by a negative cardiac history, normal physical examination, a normal electrocardiogram and a normal resting M-mode, 2-dimensional and Doppler echocardiographic study. No subjects smoked or took any medications, and none were highly trained. All subjects gave informed consent. One subject developed ventricular premature contractions during epinephrine infusions and was excluded from analysis of the epinephrine results. We therefore report on studies in 9 subjects during epinephrine infusions and on 10 subjects during atropine infusions.

Study protocol: All subjects were studied in the supine position. Intravenous catheters were inserted into the right hand and right antecubital fossa, after which the right hand and wrist were placed into a warming box (60°C), so that arterialized venous samples for catecholamine measurements could be obtained. Subjects rested in the supine position for 30 minutes after catheter insertion before baseline measurements were obtained. Epinephrine was infused at 10, 25 and 50 ng/kg/min for 12 minutes each into the antecubital vein using a Harvard pump (South Natick, Massachusetts). The epinephrine solutions were prepared by diluting epinephrine (Adrenalin chloride, Parke-Davis, Detroit, Michigan) in 0.9% saline solution to give a total infusion volume of 16 ml at each dose. Ascorbic acid (0.5 mg/ml) was added to prevent oxidation of the epinephrine. After the epinephrine infusions, the subjects rested for 30 minutes in the supine position to allow plasma levels of catecholamines and the hemodynamic state to return to baseline. After repeat baseline measures were obtained, bolus intravenous injections of atropine (atropine sulfate, Elkins-Sinn Inc., New Jersey) were given, beginning at 0.8 mg, and followed by 0.4 mg injections at 12-minute intervals until a cumulative dose of 2 mg was achieved or the heart rate was >110 beats/min.

Data collection: After the 30-minute rest, a complete Doppler study was done. Repeat Doppler and 2-dimensionally guided M-mode recordings were obtained at end-expiration during the final 2 minutes of each epinephrine infusion and atropine injection. During each Doppler acquisition, a 2-ml arterialized venous blood sample was drawn from the hand vein and processed and analyzed for plasma epinephrine and norepinephrine as previously described.[17] We have previously documented that arterialized samples obtained using a warming box correspond closely to simultaneously acquired arterial samples.[18] Blood pressures were measured at rest and every 2 minutes during the infusions using a Paramed automatic blood pressure recorder.

Echocardiography: Echocardiography was performed with a Hewlett-Packard 77020 A and recorded at a paper speed of 100 mm/s from the apical window using pulsed Doppler with auditory and visual guidance. Velocities were recorded from the area just below the mitral orifice which gave the best spectra,[19] and care was taken to obtain the smallest possible angle between the assumed blood flow and the cursor at the sampling space. The optimal transducer position was marked and used for all subsequent recordings, and care was taken to keep the sampling volume at the same location. All results were calculated as the mean of 5 digitized beats, avoiding pre- or postectopic beats. The beats with the best spectral envelopes were chosen. Peak early (E) and peak atrial (A) filling velocities (cm/s), duration of E and A in ms, and diastolic filling period (ms) were measured. The diastolic flow period was measured from onset to end of mitral inflow. In cases with no well-defined diastasis between the E and late diastolic filling peaks, the onset of arterial flow was defined as the first increase in flow velocity after the plateau or downslope of the E peak.

For assessment of systolic performance, LV outflow velocity was obtained from the apical window with continuous wave Doppler. Systolic function measures were the peak outflow velocity, determined from the outflow tract recording, and the integral of the area under the outflow curve (stroke distance).[10,11,14,20-23] M-mode echo measures of the LV end-diastolic and end-systolic diameters were obtained at end-expiration using 2-dimensional guidance at the time of each Doppler recording. The ejection fraction was calculated using the method of Teicholz.[24]

Statistical analysis: All results are given as mean ± standard deviation. Analysis of variance for repeated measures with Tukey's test for specific comparisons was used for epinephrine results. The heart rate response to individual atropine doses varied among patients. However, all subjects by design had similar heart rates at the final dose. Therefore, the data from the final dose were compared with baseline data using a paired *t* test. The total atropine dose was 1.2 mg in 2 subjects, 1.6 mg in 3 subjects and 2.0 mg in 5 subjects. The relation between the peak E, peak A, and the E/A ratio versus other variables (RR interval, diastolic filling period, duration of E and A filling, systolic measures and blood pressure) were analyzed with univariate linear regressions and forward and backward stepwise multiple regression analysis. A p value <0.05 was considered significant.

RESULTS

Atropine effects: Data from the highest atropine dose are listed in Table I. The heart rate increased by 75% (p <0.001), the diastolic filling period declined by 61% (p <0.001) and the systolic flow period was unchanged. At the final dose, there was a 23% decrease in peak E (p <0.01) and a 103% increase in the peak A (p <0.001) velocities. This resulted in a 60% decrease in the E/A ratio (p <0.001). The duration of E filling decreased by 54% (p <0.001), whereas the duration of A flow was unaltered. The reduction in peak E correlated significantly to the reduction in the diastolic filling period (r = 0.64, p <0.01) as did the increment in peak A (r = −0.95, p <0.001).

During atropine, measures of systolic function and end-diastolic diameter were unchanged (Table I). Sys-

TABLE I Effects of Final Atropine Dose on Measured Variables

Doppler Diastolic Measures	Rest	Atropine	p Value
DFP (ms)	573 ± 141	222 ± 34	0.0001
Peak E (cm/s)	77 ± 12	61 ± 11	0.001
Peak A (cm/s)	40 ± 6	81 ± 17	0.001
Dur. E (ms)	239 ± 20	111 ± 43	0.001
Dur. A (ms)	126 ± 9	113 ± 16	NS
E/A	2.0 ± 0.5	0.8 ± 0.3	0.0001
E/A/DFP	3.5 ± 0.6	3.6 ± 0.6	NS
Systolic measures and end-diastolic dimension			
SFP (ms)	294 ± 22	236 ± 19	NS
M-mode EF (%)	70 ± 6	68 ± 6	NS
Peak Ao outflow (cm/s)	98 ± 12	102 ± 10	NS
Stroke distance (m)	0.144 ± 0.16	0.118 ± 0.014	NS
EDD (cm)	4.9 ± 0.4	4.7 ± 0.5	NS
RR interval and blood pressure			
RR (ms)	987 ± 171	579 ± 42	0.001
Systolic BP (mm Hg)	121 ± 8	125 ± 7	NS
Diastolic BP (mm Hg)	66 ± 6	73 ± 9	0.07
MAP (mm Hg)	83 ± 7	89 ± 9	NS
Plasma catecholamines			
Norepinephrine (pg/ml)	190 ± 56	190 ± 64	NS
Epinephrine (pg/ml)	102 ± 40	105 ± 44	NS

Ao = aortic; BP = blood pressure; DFP = diastolic filling period; Dur. A = duration of atrial filling; Dur. E = duration of early filling; E/A = E:A ratio; E/A/DFP = E:A ratio divided by DFP; EDD = end-diastolic dimension; EF = ejection fraction; MAP = mean arterial pressure; NS = not significant; Peak A = peak atrial filling velocity; Peak E = peak early filling velocity; SFP = systolic flow period.

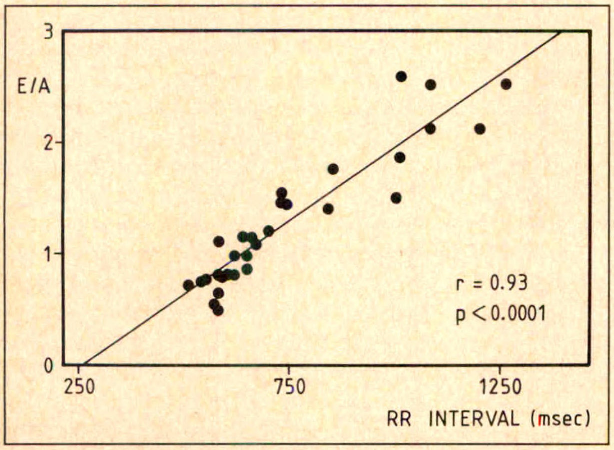

FIGURE 1. The early:atrial (E/A) ratio at all heart rates in all subjects during atropine administration.

tolic blood pressure was unchanged, diastolic pressure increased slightly ($p = 0.07$) and the mean arterial pressure was unchanged. Plasma catecholamines were also unchanged.

There was a highly significant correlation between the E/A and RR interval ($r = 0.93$, $p < 0.0001$), and also between the E/A and the diastolic filling period ($r = 0.98$, $p < 0.0001$) (Figure 1). In multiple stepwise regression analysis, no other variable entered at the $p < 0.05$ level. Thus, atropine effects appeared to be primarily mediated by heart rate or diastolic filling period changes. To determine whether heart rate effects can be normalized, we divided the E/A ratio by the RR interval (Figure 2A) and by the diastolic filling period (Figure 2B). Only the diastolic filling period appeared to normalize for heart rate changes, because the E/A/RR interval remained significantly correlated to heart rate

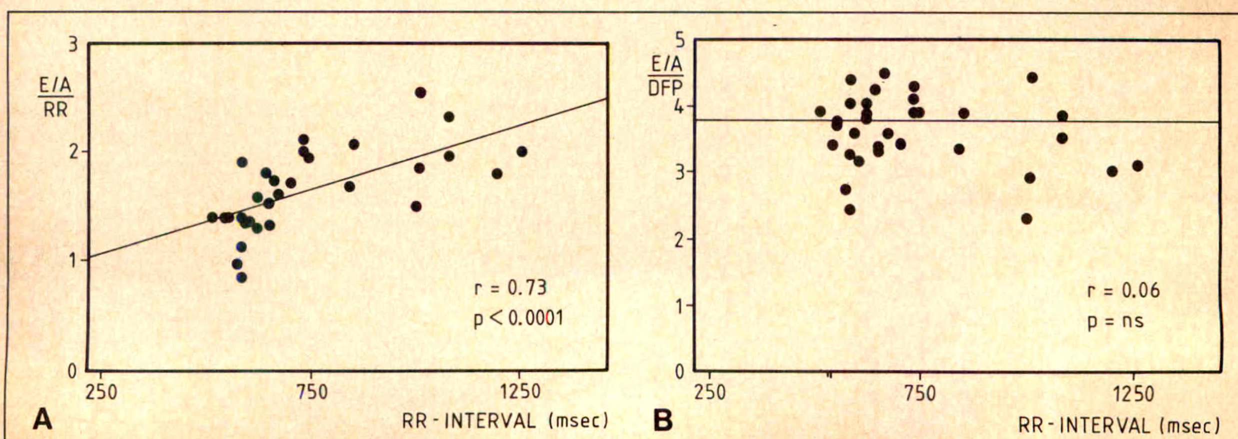

FIGURE 2. *A*, the early:atrial (E/A) ratio normalized by the RR interval, and *B*, the E/A ratio normalized by the diastolic filling period (DFP).

TABLE II Effects of Epinephrine on Diastolic and Systolic Measurements

	Rest	ng/kg/min 10	25	50	p Value*
Diastolic measures					
DFP (ms)	596 ± 144	579 ± 156	512 ± 111	464 ± 127	0.004
Peak E (cm/s)	79 ± 12	93 ± 8	102 ± 10	113 ± 16	0.001
Peak A (cm/s)	40 ± 6	44 ± 7	49 ± 12	52 ± 9	0.01
Dur. E (ms)	233 ± 27	242 ± 33	234 ± 47	222 ± 57	NS
Dur. A (ms)	130 ± 18	128 ± 12	128 ± 10	126 ± 7	NS
E/A	2.0 ± 0.5	2.1 ± 0.4	2.2 ± 0.6	2.3 ± 0.6	0.13
E/A/DFP	3.5 ± 0.6	3.2 ± 0.6	4.3 ± 0.8	5.0 ± 1.3	0.009
Systolic measures and end-diastolic dimension					
M-mode EF (%)	66 ± 6	71 ± 6	78 ± 3	83 ± 5	0.02
Peak Ao (cm/s)	95 ± 17	107 ± 14	124 ± 21	44 ± 25	0.01
Stroke distance (m)	0.14 ± 0.02	0.15 ± 0.02	0.18 ± 0.02	0.20 ± 0.03	0.07
EDD (cm)	4.9 ± 0.3	4.9 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	NS
RR interval and blood pressure					
RR (ms)	1026 ± 172	986 ± 158	900 ± 129	820 ± 141	0.001
Systolic BP (mm Hg)	120 ± 4	121 ± 7	127 ± 10	134 ± 9	0.009
Diastolic BP (mm Hg)	62 ± 6	58 ± 8	53 ± 9	47 ± 7	0.01
MAP (mm Hg)	82 ± 3	78 ± 6	78 ± 6	75 ± 6	0.05
Plasma catecholamines					
Norepinephrine (pg/ml)	196 ± 47	277 ± 76	332 ± 86	368 ± 96	0.01
Epinephrine (pg/ml)	94 ± 59	318 ± 94	614 ± 54	879 ± 310	0.01

* p value for 50 ng/kg/min versus rest.
Abbreviations as in Table I.

(r = −0.73, p <0.001), whereas the E/A/diastolic filling period was not (r = 0.06, difference not significant [NS]).

Epinephrine effects: As expected, epinephrine caused dose-dependent changes in systolic function as measured by M-mode ejection fraction and by Doppler (Table II). At the high dose, ejection fraction increased by 26% (p <0.01), peak outflow velocity increased by 52% and stroke distance increased by 38% (p <0.001). Systolic pressure increased while diastolic and mean arterial pressure decreased. At the high dose, epinephrine caused a 26% increase in heart rate (p <0.01) and a 22% reduction in diastolic filling period (p <0.01) (Table II). Despite the increased heart rate, peak E increased by 43% (p <0.001), peak A increased by 30% (p <0.01) and the E/A ratio increased by 15% (p = 0.13). The E/A/diastolic filling period increased by 43% (p <0.001) (Figure 3).

Correlations between epinephrine-induced changes and other hemodynamic variables (Table III): In univariate analyses incorporating all epinephrine infusions, plasma epinephrine levels were significantly correlated with the E peak (r = 0.74, p <0.001), A peak (r = 0.59, p <0.001) and the E/A/diastolic filling period (r = 0.59, p <0.001) but not with the E/A ratio (r = 0.04, NS).

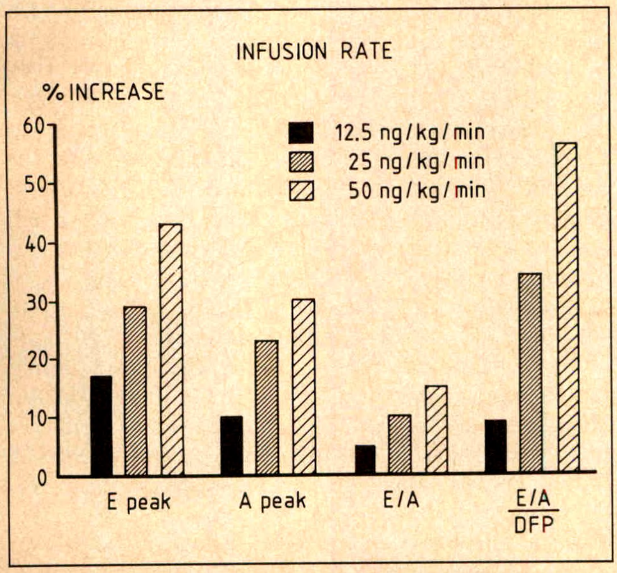

FIGURE 3. The relative increments (percent increase from baseline) in the peak early (E) velocity, the peak atrial (A) velocity, the E/A ratio and the E/A/diastolic filling period (DFP) at the 3 epinephrine infusions.

TABLE III Univariate Correlations to Diastolic Filling Velocities During Epinephrine Infusions

	E Peak	A Peak	E/A	E/A/DFP
Plasma catecholamines				
Epinephrine	0.74*	0.58*	0.04	0.59*
Norepinephrine	0.47†	0.11	0.29	0.51*
Timing measures				
RR	−0.19	−0.67*	0.25	−0.60*
DFP	−0.09	−0.70*	0.27	−0.50†
Dur. E	−0.17	−0.27	0.14	0.14
Dur. A	−0.27	0.06	−0.12	0.05
Systolic function measures				
M-mode EF	0.70*	0.40‡	0.18	0.70*
Peak Ao	0.69*	0.67*	0.07	0.55*
Stroke distance	0.78*	0.46†	0.17	0.51*

* p <0.001; † p <0.01; ‡ p <0.05.
Abbreviations as in Table I.

Peak E velocity was strongly correlated with all 3 systolic measures, but was not correlated with measures that reflected timing of cardiac events (RR interval, diastolic filling period, duration of E and A filling velocities). The peak A velocity significantly correlated with all 3 systolic measures as well as with the timing measures, particularly the diastolic filling period.

There were no significant univariate correlates between the uncorrected E/A ratio and the timing measures, and systolic function or catecholamine levels. In contrast, in univariate analyses the normalized E/A (E/A/diastolic filling period) correlated closely to the ejection fraction ($r = 0.70$, $p <0.001$), to the epinephrine level ($r = 0.59$, $p <0.01$) and to the stroke distance ($r = 0.51$, $p <0.01$). In forward and backward stepwise regression analyses, in which all systolic measures and blood pressure were allowed to enter, the E/A ratio correlated to the diastolic filling period ($r = 0.72$, $p <0.001$) and ejection fraction ($r = 0.58$, $p <0.01$), whereas the only significant correlate to the normalized E/A ratio (E/A/diastolic filling period) was the M-mode ejection fraction ($r = 0.65$, $p <0.001$).

DISCUSSION

Doppler-derived transmitral filling velocities are widely, but potentially erroneously, used as measures of diastolic function. A variety of different factors may have opposing effects on such filling velocities.[1-5] The current study investigated the influence of parasympathetic withdrawal induced by atropine and sympathetic stimulation induced by epinephrine on Doppler measurements of LV filling velocities in young normal men. Our results indicate that parasympathetic withdrawal induced marked changes in LV filling velocities, which were tightly correlated to changes in heart rate and diastolic filling period. Our results also document that epinephrine causes highly significant and dose-dependent changes in diastolic filling parameters.

Atropine effects: At the highest atropine dose, parasympathetic withdrawal caused a significant 21% reduction in peak E and a 103% increase in peak A. These changes resulted in a 60% decrease in the E/A ratio. Several factors, other than heart rate, that are known to alter diastolic filling velocities were examined and were found not to change during atropine. The stability of the catecholamine levels suggests that sympathetic activation, which can influence diastolic function, did not occur. Systolic function was also unchanged. Furthermore, the lack of change in blood pressure suggests that changes in afterload did not account for the observed effects.

The increased heart rate and reduced diastolic filling period appeared to be of primary importance in altering filling velocities, as suggested by the multiple regression analysis. Atropine infusion led to a 41% decrease in the RR interval. The reduction in cardiac cycle length was mostly at the expense of diastolic filling, which decreased by 61%, whereas the systolic emptying period did not change significantly. Furthermore, the shortening of the diastolic filling period was largely at the expense of the E filling period which declined by 54%, whereas the A filling period was unchanged. The increase in peak A was highly correlated to the shortening of the E filling period ($r = -0.93$) suggesting that the increase in peak A was partially a compensation for a reduction in E filling.

Prior cross-sectional studies have suggested a correlation between the resting heart rate and measurements of diastolic function.[1,5] This study noted that during a decrease in RR interval of 700 ms, the E/A ratio decreased from 2.0 ± 0.5 to 0.8 ± 0.3. Thus, for each 100 ms reduction of the RR interval, the E/A ratio decreased by approximately 0.29 units in these young normal subjects. This heart rate–induced change in the E/A ratio may explain some of the previously described differences in the E/A ratio among patient groups. For example, Zarich et al[25] noted an uncorrected E/A of 1.66 in normal subjects and 1.24 in diabetic patients, who had a mean heart rate of 13 beats/min faster than the normal subjects. Based on our data, if the normal group had the same heart rate as the diabetic group, the heart rate–normalized E/A ratios of the normal subjects (1.31) would have been similar to those in the diabetics (1.24). Similarly, Vandenberg et al[16] concluded that dobutamine did not alter the E/A ratio (1.96 to 2.15, NS) in a group of 7 subjects aged 24 to 28 years. However, if the 11 beat/min increase in heart rate was accounted for, the E/A ratio increased from approximately 1.96 to 2.59, which is in accordance with the epinephrine results in the current study. Thus, heart rate differences may mask changes that are present, or conversely, suggest changes that are not present after heart rate effects are accounted for. In the current study, when the E/A ratio was normalized by dividing by the diastolic filling period, the observed changes due to increased heart rate seemed to disappear. The E/A ratio normalized by the diastolic filling period (E/A/diastolic filling period) did not correlate with heart rate ($r = 0.06$, NS) or the diastolic filling period ($r = 0.10$, NS). In contrast, the E/A ratio normalized by the RR interval correlated significantly with both the heart rate ($r = -0.73$) and the diastolic filling pressure ($r = 0.72$). These data suggest that the effects of heart rate can best be normalized by dividing the E/A ratio by the diastolic filling period rather than by the RR interval (Figure 2, A and B). This may be due in part to the fact that most of the reduction in RR interval was due to a decrease in the diastolic filling period. Whether such normalizations apply to elderly subjects or to patients with heart disease needs to be determined.

Epinephrine effects: Epinephrine caused substantial dose-dependent increments in diastolic filling velocities (Figure 3). There were marked increases in E and A filling velocities and the ratio between peak E and A filling normalized for the diastolic filling period. Thus, during epinephrine infusions, E peak, E/A and E/A/diastolic filling period showed alterations opposite in direction to those induced by atropine, despite the significant increase in heart rate that occurred with epinephrine.

Whereas epinephrine caused a minor reduction in mean arterial pressure, the preload as assessed by end-diastolic dimension was unchanged. Therefore, changes in loading conditions are unlikely to have caused the observed alterations in diastolic filling velocities.

Previous studies using a variety of measures have noted variable results with sympathetic stimulation. Vandenberg et al[16] reported a nonsignificant increase in the E/A ratio during dobutamine administration, which would have been more apparent had they normalized for heart rate changes. Colan et al[26] found a uniform and dramatic increase in the peak rate of LV dimension enlargement with a moderate increase in heart rate using dobutamine. In an exercise study, Held et al[15] reported a decrease in the E/A ratio after upright exercise, at a time when sympathetic activation is increased. However, the heart rate increased from 81 to 119 beats/min during the intervention. If "normalized" for the simultaneous decrease in diastolic filling pressure, their results were comparable to our findings with epinephrine. In fact, their normalized E/A ratio increased from approximately 3.8 to 5.5. Thus, the changes in diastolic filling velocities induced by epinephrine in the current study are similar to the changes that occur with exercise.[15]

During the epinephrine infusions, there were dose-dependent increases in systolic function measures. M-mode ejection fraction, stroke distance and peak aortic outflow velocity increased substantially. The latter has been shown to accurately reflect the contractile state in normal hearts,[11,21-23] and the change in systolic function is in accord with results from similar previous studies both from our laboratory and from others.[9,11,14]

Study limitations: Diastolic filling is a complex phenomenon that is influenced by multiple factors. Several measures can be used to characterize it. Our study was limited to measures of transmitral filling velocities and time intervals. The extent to which these accurately reflect invasively measured diastolic properties such as compliance and stiffness is unclear. Loading conditions influence diastolic function and they were only measured noninvasively and indirectly in the present study. The pressure gradient between the left atrium and the left ventricle determines, in part, filling velocities.[27-30] No intracardiac pressures were measured in the current study because we found it to be unacceptable to do invasive studies in a healthy study group. We studied only men, but a previous report did not find any gender influence on the Doppler filling velocities.[30] The location of the sampling site may influence the measurement of filling velocities. We used a constant location for the sampling volume. Because these studies were conducted in unanesthetized, unblocked humans, the observed effects were due to both the primary effects of atropine and epinephrine as well as any secondary reflex activation that occurred.

Despite these limitations, this study offers evidence that parasympathetic withdrawal causes a reduction in peak E, a marked increase in peak A and a resultant reduction in the E/A ratio. These changes are mainly due to changes in heart rate and diastolic filling period. Heart rate-induced changes in the E/A ratio were normalized by dividing the E/A by the diastolic filling period in these young healthy subjects. Epinephrine, at physiologic levels, increases peak E, peak A and the E/A ratio normalized by the diastolic filling period. These results document the major effects of parasympathetic withdrawal and β-adrenergic stimulation on filling velocities in young normal subjects. We conclude that these factors are important variables that must be taken into account if transmitral Doppler velocities shall be useful measures of diastolic filling.

Acknowledgment: We gratefully acknowledge the expert technical assistance of Miles Matsuda, Jean Hadlock, Kevin Murphy and Candy Sands. We also thank James Kousbaugh for preparation of the manuscript.

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Effects of Aminophylline on Atrioventricular Conduction in Patients with Late Atrioventricular Block During Inferior Wall Acute Myocardial Infarction

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Two recent case reports[1,2] have suggested a possible role of aminophylline in reversing atrioventricular (AV) block occurring during inferior wall acute myocardial infarction (AMI). This report examines the effect of aminophylline on AV block in a large group of patients with inferior AMI.

Fifteen consecutive patients with inferior wall AMI who developed second-degree or complete AV block were included in this study (Table I). Patients had to maintain a stable AV block rhythm for at least 1 hour before aminophylline administration. Patients with AV block who were receiving drugs known to depress AV nodal conduction were excluded (e.g., digitalis, β blockers, calcium channel blockers, amiodarone). Patients who developed AV block during the hyperacute phase of the inferior AMI were also excluded because this early-appearing AV block in our experience tends to disappear abruptly and rapidly parallel to the disappearance of the superacute ischemia. Therefore, only patients with "late" block were included.[3]

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Inferior AMI was diagnosed by the triad of typical chest pain lasting >20 minutes, evolutionary ST-T changes with development of pathologic Q waves in the inferior leads and an increase in serum cardiac enzymes. Aminophylline was given as a loading dose of 7 mg/kg infused over 20 minutes (serum levels were not measured). Patients were monitored throughout the infusion period. Electrocardiographic rhythm strips were obtained before and 5 minutes after drug administration and the type of AV block and the atrial and ventricular rate noted. Blood pressure was monitored by arm cuff.

There were 11 men and 4 women whose ages ranged from 52 to 85 years (mean 71 ± 8). AV block was late in appearance (by protocol) in all patients, starting 2 to 6 days after the hyperacute stage of AMI. The type of AV block was of second-degree Wenckebach type in 5 patients, 2:1 AV block in 6 patients and complete in 4 patients. All patients had narrow QRS complexes. At the time of aminophylline administration only 2 patients had a temporary pacemaker installed. In both, the pacemaker was switched off for the hour of observation before and throughout the time of drug administration.

The mean sinus rate before aminophylline was 90 ± 11 beats/min and decreased to 85 ± 13 after drug administration (p <0.02). There were no significant changes

TABLE I Clinical Characteristics and Response to Aminophylline

Pt. No.	Age (yr) & Sex	AV Block Appearance (days)	Degree of AV Block C	Degree of AV Block A	Atrial Rate C–A	Ventricular Rate C–A
1	77M	3	W 3:2	W 3:2	70–65	60–60
2	80M	3	W 3:2	1:1 PR:0.30	78–70	58–70
3	62F	2	W 5:4	W long cycle	92–70	80–60
4	85M	2	W 3:2	W 3:2	75–70	55–50
5	76F	3	W 7:6	1:1 PR:0.28	90–90	70–90
6	64M	5	2:1	W 3:2	95–92	60–70
7	71M	6	2:1	2:1	98–102	49–51
8	76M	4	2:1	2:1	100–100	50–50
9	72F	3	2:1	2:1	90–90	45–45
10	73M	2	2:1	2:1	80–80	40–40
11	73M	6	2:1	2:1	80–80	40–40
12	66M	3	Com.–AV dis.		100–78	72–81
13	62M	5	Com.–Com.		90–84	36–41
14	52M	4	Com.–Com.		105–92	53–57
15	72F	2	Com.–Com.		110–110	30–30
Mean ± SD	71 ± 8				90 ± 11–85 ± 13 p <0.02	53 ± 14–55 ± 16 p >0.1

A = aminophylline; AV = atrioventricular; C = control; Com. = complete; dis. = dissociation; SD = standard deviation; W = Wenckebach.

in the ventricular rate, from 53 ± 14 to 55 ± 16 beats/min. Of the 5 patients with Wenckebach-type second-degree AV block, 2 recovered 1:1 AV conduction with long PR intervals (0.30 and 0.28 second, respectively), 1 continued to have Wenckebach block but with longer cycles of block and the remaining 2 had no changes. Of the 6 patients with 2:1 AV block, 5 had no change in conduction. The remaining patient changed from 2:1 block to a 3:2 Wenckebach sequence. Of the 4 patients with complete AV block, an acceleration of the junctional escape rhythm was noted in 3, and in 1 of them the acceleration of the junctional rhythm was above the sinus rate, therefore causing temporary AV dissociation due to junctional acceleration. No adverse effects were noted from the administration of aminophylline.

The incidence of second- and third-degree AV block in patients with inferior AMI is well known and ranges between 10 to 30%.[4,5] However, its pathophysiology has not been properly established. Acute ischemia, increased parasympathetic activity and ischemic metabolites with negative dromotropic effects have been implicated in the development of AV block.[5]

Several studies have classified the AV blocks occurring during inferior AMI according to the time of appearance of the AV block (early versus late block). These studies have shown contradictory results. For example, Feigl et al[6] reported that AV block occurring early in the course of inferior AMI is atropine-responsive, and was likely to be due to vagotonia, compared with a more delayed onset of AV block, which tends to be atropine-resistant and more likely secondary to AV node ischemia. We have found opposite results.[3] In our group with early AV block, 36% of patients responded to atropine, whereas in the group with late AV block, 77% responded to atropine. We hypothesized that the appearance of AV block observed in the very early period of AMI (hyperacute stage) is related to severe and transient ischemia of the AV node, whereas AV block occurring during the subsequent stages of the infarct (late block) may be related to an increased release of metabolites that slow AV nodal conduction, such as potassium and adenosine.

In this context, 2 recent case reports tested the efficacy of aminophylline in reversing AV block in 3 patients with atropine-resistant AV block occurring in the late phase of the AMI (late block).[1,2] Aminophylline, a competitive antagonist of the dromotropic effects of adenosine, improved AV conduction in all 3 patients, suggesting metabolic etiology in at least some cases of AV block. In this study we prospectively evaluated the effect of aminophylline in 15 patients with inferior AMI who developed "late block." We found a facilitation of AV conduction in 3 of 5 patients with a Wenckebach type of second-degree AV block. In patients with a higher degree of AV block, such as 2:1 or complete AV block, no beneficial effects were noted. It seems that in milder degrees of AV block, aminophylline may exert salutatory effects on AV conduction, whereas in more advanced degrees of block, no effect can be seen. There are several explanations to our results. First, these late AV blocks are caused by the release of adenosine and potassium, with different degrees of block representing different concentrations of the released metabolites. Aminophylline in the dosage given was able to antagonize only mild cases. Second, these late AV blocks are not caused by the release of metabolites, and in the few cases in which we saw an improvement in AV conduction, this was due to the sympathomimetic action of aminophylline.[1] We did not measure aminophylline levels, however; we gave similar doses as in previous case reports. At these dosages, the serum concentration of aminophylline is below the threshold concentration required to release catecholamines or increase tissue cyclic adenosine monophosphate content.[7] In addition, in this concentration range, plasma catecholamines were not changed by theophylline.[8] As noted also by Wesley et al,[1] sinus cycle lengths either did not change or actually lengthened after aminophylline, thus arguing against a sympathomimetic action. Only in patients with complete AV block did we see an increase in the junctional escape rate, suggesting a possible sympathetic action. Our study suggests that aminophylline improves AV conduction in some patients with late AV block complicating inferior AMI. Patients with the greatest chance of improving are those with milder degrees of AV block and therefore with the lesser need for therapy. Further studies are needed to elucidate the possible role of aminophylline in early AV blocks and in possible subgroups of late AV blocks, such as atropine-resistant or responsive AV block.

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Detection of Myocardial Viability in Stunned or Hibernating Myocardium by Delayed Emptying on Radionuclide Ventriculography

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In regions of myocardium with absent or severely depressed contractile function, differentiation between necrotic and either stunned or hibernating myocardium (viable tissue) can be difficult, and is now a common clinical problem. Although myocardial stunning and hibernation are different processes, function can improve in both: after the passage of time in the former[1] and after revascularization in the latter.[2,3] Both share the property of residual contractile activity[1–6] which can be demonstrated by inotropic stimuli[4,5] or after nitroglycerin.[4,6] Recently, postsystolic shortening has been shown to predict late recovery of contractile function in akinetic segments after acute coronary occlusion in a canine model of stunned myocardium.[7–9] We postulate that regional delay in peak emptying on radionuclide ventriculography could detect this phenomenon noninvasively and thereby provide a marker of myocardial viability in dysfunctional regions which are either stunned or hibernating. This report describes the radionuclide technique and results of revascularization in 7 patients with delayed emptying on preoperative radionuclide ventriculography.

Over a 9-month period, we identified delayed emptying on radionuclide ventriculography in 7 patients scheduled for revascularization (Table I). In 3, tardokinesia[10] or postsystolic contraction was seen on the radionuclide ventriculogram, and in all 7, the question of viability was raised clinically. No patient had bundle branch block on the electrocardiogram. Two patients were studied <1 week after an acute anterior infarction: 1 Q-wave (patient 2) and 1 non-Q-wave infarction (patient 6, Table I). Another 2 were studied ≤2 weeks after acute anterior Q-wave infarction (patients 3 and 5). Of the remaining 3 patients, 1 had sustained an anterior Q-wave infarction 8 weeks previously (patient 4), whereas the other 2 had no history of anterior wall infarction and were studied because of recurrent left ventricular failure (patient 7) or unstable angina (patient 1).

All patients underwent radionuclide ventriculography before revascularization, and repeat radionuclide ventriculography 1 to 9 months after revascularization (mean 3.9 months). The patients had been considered for revascularization before entering the study on the basis of either recurrent chest pain or ischemia on thallium studies. All had severe regional depression (akinesia or severe hypokinesia) of anterolateral or apical wall motion, or both, on contrast left ventriculography. Clinical details and results of coronary angiography are listed in Table I. Coronary angiograms were graded visually by an angiographer blinded to the radionuclide data, and revealed ≥90% diameter reduction of the left anterior descending coronary artery in every patient. Coronary bypass surgery was performed in 6 patients, and 1 had balloon angioplasty.

Red blood cell labeling was performed using the in vivo technique with intravenous injection of 10 μg/kg stannous ion and 750 MBq of technetium-99m pertechnetate. Studies were performed using a small field-of-

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TABLE I Clinical Details, Timing of Radionuclide Ventriculography and Coronary Angiography, and Results of Coronary Angiography and Contrast Ventriculography

Pt. No.	Age (yr) & Sex	Q-wave AMI	AMI Site	Interval AMI to RNVG (weeks)	Interval AMI–CA (weeks)	Percent Diameter Reduction at Coronary Angiography: Right	LM	LAD	LC	Contrast Ventriculogram	Interval Revascularization to Second RNVG (mos)	Delay in Peak Emptying (ms)
1	42M	+	Inferior	—	—	—	—	90	—	Apical severe hypokinesia	1.5	160
2	44M	+	Anterior	<1	<1	—	—	90	90	Apical akinesia Anterolateral severe hypokinesia	2	180
3	45F	+	Anterior	2	2	—	—	99	50	Apical akinesia	2.5	90
4	56M	+	Anterior	8	8	—	—	99	—	Apical severe hypokinesia	3	250
5	60F	+	Anterior	2	2	—	—	90	—	Apical severe hypokinesia	8	120
6	60M	Non-Q	Anterior	1	1	—	—	99	—	Apical akinesia	9	200
7	62M	—	—	—	—	—	—	90	—	Apical severe hypokinesia Anterolateral severe hypokinesia	1	150

AMI = acute myocardial infarction; CA = coronary angiography; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LM = left main coronary artery; Non-Q = non-Q-wave AMI; right = right coronary artery; RNVG = radionuclide ventriculography.

view mobile gamma camera with a low-energy all-purpose 30° slant hole collimator to maximize visual separation of atria and ventricles. A parallel hole collimator was used for the anterior and left lateral views, and a 30° slant hole collimator for the left posterior oblique view. Data acquisition was synchronized to the electrocardiogram using 24 frames for the left anterior oblique view, and 16 frames for the other 3 views. Time-activity curves for the left ventricular blood pool were obtained for the left anterior oblique view using semiautomatic definition of the left ventricular region at different stages of the cardiac cycle.[11] Background activity was estimated from a region of interest outside the apical and lateral walls.

The parametric image of time to peak emptying was obtained for the left anterior oblique view based on a 3-component Fourier analysis of the left ventricular region,[12] and used to identify the abnormal segment. This image demonstrated an area of synchronous delay in time to peak emptying, out of phase with the remainder of the ventricle, in all patients. An example is shown in Figure 1. Regions of interest were drawn over the abnormal and normal segments, and background-corrected time-activity curves produced for the normal and abnormal segments (Figure 1). Delayed emptying was defined as a clearly identified delay >80 ms between troughs of the 2 curves. In the canine model,[9] the best correlate of early return of regional systolic function was total shortening (regional postsystolic plus systolic shortening, referenced to global end-systole). This corresponds with total regional emptying (postsystolic plus systolic emptying) in the abnormal segment on radionuclide ventriculography, as illustrated in Figure 1.

Regional wall motion was assessed before and after revascularization by a consensus of ≥2 experienced observers blinded to the other data, to determine whether improvement had occurred. A visual analog wall motion score (0 = normal, 1 = mild hypokinesia, 2 = moderate hypokinesia, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia) was given to each of 5 regions: septum, apex, anterior, lateral and inferior walls. Regional ejection fraction was calculated by a semiautomated technique dividing the ventricle into 6 regions relative to the long axis of the ventricle at end systole.[11] This has been expressed as standard deviation from the normal range derived in our laboratory. Global ejection fraction was also calculated using a standard technique.[11] Paired t tests were used to compare mean wall motion scores and ejection fraction before and after revascularization. A p value <0.05 was considered statistically significant.

All 7 patients had an apical region of synchronous delayed emptying on the parametric image of time to peak emptying, which extended to the ventricular septum in 6. The regional time-activity curves of the abnormal segments demonstrated continued reduction in counts after global end-systole in all 7 patients. An example is shown in Figure 1. In all patients, the postsystolic plus systolic decrease in counts below end-diastolic counts (total emptying) exceeded the systolic increase in counts in the abnormal area (Figure 1). The mean time delay in emptying between normal and abnormal areas was 170 ± 50 ms. Individual values are listed in Table I.

Revascularization was clinically unsuccessful in 1 patient (no. 4) who underwent balloon angioplasty to the left anterior descending coronary artery, and sustained an extension of his previous anterior infarction. The remaining 6 patients had an uncomplicated perioperative course after coronary artery bypass surgery.

Figure 2 details the changes in regional wall motion for each patient. In the 6 patients with uncomplicated bypass surgery there was an improvement in apical regional wall motion score of ≥3, with the mean score decreasing from 3.8 ± 0.8 to 0.7 ± 0.8 ($p < 0.01$). Septal

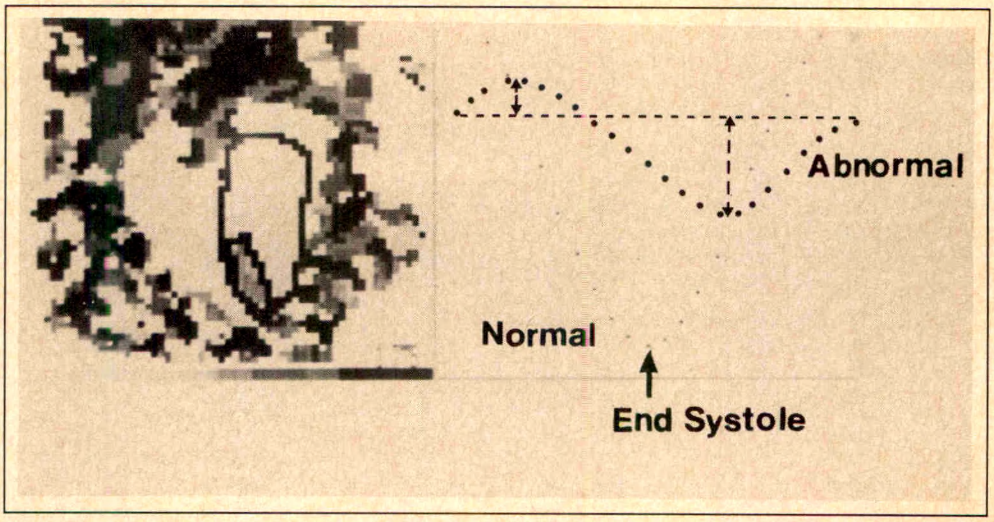

FIGURE 1. Parametric image of time to peak emptying in left anterior oblique view from the preoperative radionuclide ventriculogram. The abnormal area with a delayed time to peak emptying extending from apex into the septum has been shaded and outlined as the abnormal region of interest. Time-activity curves on the *right* from the normal and abnormal areas show a 200-ms delay in emptying of the abnormal area after global end systole. Compared with end-diastolic counts *(horizontal dashed line)*, the small systolic increase in counts (*small vertical dashed line on left* = dyskinesia) is less than the decrease in counts in the abnormal region (*large vertical dashed line on right* = total emptying).

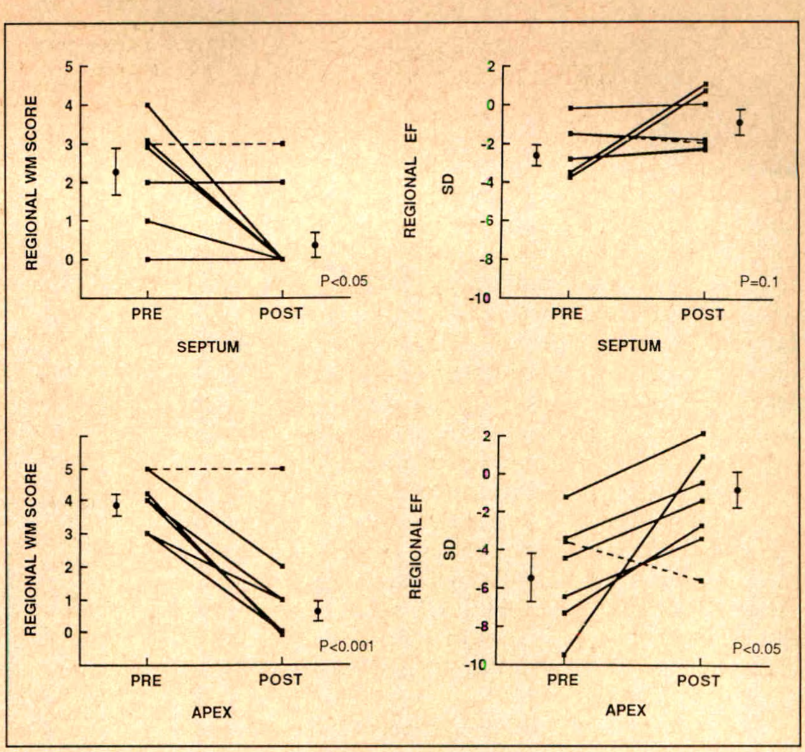

FIGURE 2. Regional left ventricular function assessments from radionuclide ventriculography in individual patients before (PRE) and after (POST) operation. *Top 2 panels,* indexes derived from the septum; *lower 2 panels,* indexes derived from the apex; *left,* regional visual wall motion (WM) scores (range 0 to 5); *right,* regional ejection fraction (EF) in standard deviation (SD) units from the mean of the normal range. Values for individual patients are joined by *solid lines. Dashed line* indicates the patient with unsuccessful angioplasty in whom regional function deteriorated after revascularization. To the *left* and *right* are mean ± standard error bars for the 6 patients with successful revascularization. P values are for paired *t* tests comparing results before and after operation in the 6 patients with successful revascularization.

scores improved ≥3 in 3 of the 6 patients, with the mean score decreasing from 2.2 ± 1.5 to 0.3 ± 0.8 (p <0.05). Apical ejection fraction improved ≥2 standard deviations (from the normal range) in all 6 patients, with a significant mean improvement from −5.4 ± 3.0 to −0.8 ± 2.2 (p <0.05). Septal ejection fraction changed from −2.4 ± 1.3 to −0.7 ± 1.6, but this was not significant. The global ejection fraction improved ≥5% in 4 of the 6 patients, with the mean ejection fraction improving from 47 ± 12% to 58 ± 6%, p <0.05 (Figure 3). The patient with the worst global function had a large improvement, from 28 to 51%. The patient with unsuccessful angioplasty showed a deterioration in regional wall motion score of the anterior wall, as well as a worsening of regional apical and global ejection fractions, indicating that this myocardial region may have been viable before attempted revascularization.

After revascularization, all 6 patients with uncomplicated bypass surgery had normal parametric images of time to peak emptying, with no areas of delay. The patient in whom angioplasty was not successful had a persistent regional delay in time to peak emptying.

These results suggest that the phenomenon of postsystolic shortening, which predicts viability in a canine model of infarction,[8,9] can be detected noninvasively by radionuclide ventriculography in patients with coronary artery disease. Synchronous regional delay in emptying can be readily appreciated in parametric images of time to peak emptying, with regional time-activity curves demonstrating delay in the nadir of counts compared to end-systole in the normal regions. This noninvasive demonstration of postsystolic shortening in areas with severely reduced or absent systolic contractile function on contrast ventriculograms identified myocardial segments that were viable and that could show improved systolic function after successful revascularization.

This technique does not differentiate between stunned and hibernating myocardium, which may be relevant in 4 of the patients studied soon after infarction. While stunning may have contributed to the wall motion abnormality in these 4 patients, all 4 had severe residual stenoses in the infarct-related artery of sufficient severity to produce chronic ischemia and hibernation. It is likely, however, that the phenomenon of delayed emptying may be applied to predict viability and potentially recoverable func-

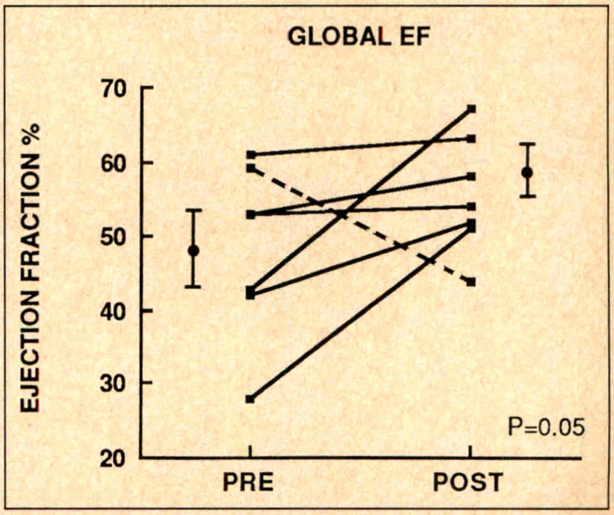

FIGURE 3. Global left ventricular ejection fraction for the individual patients before (PRE) and after (POST) operation. Mean global ejection fraction (EF) in the 6 patients with successful revascularization increased significantly after revascularization. See legend for Figure 2.

tion in both stunned and hibernating myocardium, as the property of residual contractile function appears to be shared by both.[1-3]

This study was confined to patients with abnormalities of wall motion in the distribution of the left anterior descending coronary artery, affecting the septum, apex or anterolateral wall, since the parametric analysis of time to peak emptying was performed only on the left anterior oblique view. Further studies would be required to assess whether this technique was applicable to inferior or posterior wall motion abnormalities. Another potential limitation of this method is the differentiation of active postsystolic contraction from passive elastic recoil in areas composed of necrotic or scar tissue. In the canine model, there was no relation between systolic lengthening (dyskinesia) and postsystolic shortening, indicating this is not likely due to passive recoil.[8,9] In all our patients, there was a substantial decrease in counts below end-diastolic counts in the abnormal segment, to a minimum after global end-systole (total empyting, Figure 1), which exceeded the systolic increase in counts (dyskinesia) in that segment. This would be in favor of an active but delayed contractile process.

We conclude that the phenomenon of postsystolic shortening may be detected noninvasively by delayed emptying on radionuclide ventriculography. This appears to be a promising technique for the identification of residual viable myocardium in akinetic or severely hypocontractile regions that can improve after successful revascularization. Further studies are needed to determine the sensitivity and specificity of the finding and its clinical applicability.

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Prognostic Significance of Hydropericardia and Pericardial Friction Rub in Q-Wave Acute Myocardial Infarction

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It is generally agreed that a pericardial friction rub or a pericardial effusion is not associated with increased hospital mortality during acute myocardial infarction (AMI).[1-5] Because a pericardial friction rub has been reported as a noninvasive sign of pericardial inflammation, irrespective of whether it is associated with a pericardial effusion, we hypothesized that the clinical course of patients with a pericardial effusion without a pericardial friction rub (hydropericardia) is different from that of patients with a pericardial friction rub. In this investigation, hydropericardia and pericardial friction rub were evaluated along with 8 other clinical factors that may affect hospital mortality to determine the prognostic importance of each factor in patients with a first Q-wave AMI.

We studied 330 consecutive patients with a first Q-wave AMI (anterior wall, 203; inferior wall, 127) who were admitted to the coronary care unit within 24 hours from the onset of chest pain and who survived the first 3 days after admission. It is a routine procedure in our hospital to insert a Swan-Ganz catheter in patients with an AMI admitted within 24 hours from the onset of chest pain. All patients were examined by a physician, and written informed consent was obtained before the Swan-Ganz catheter insertion. No patient had chronic renal failure, collagen disease, cardiac surgery within the previous 6 months, or metastatic disease. Technically satisfactory echocardiograms could not be obtained in 37 patients, and they were not included in this study.

The diagnosis of AMI was made when patients had an ST elevation with new Q waves (anterior wall, ≥2 in V_{1-6}; inferior wall, leads II, III and aVF) in serial electrocardiograms and ≥2 times the normal elevation in the level of serum creatine kinase with MB isoenzyme >5%. All patients were examined by careful auscultation ≥2 times per day. Pericardial friction rub was considered as a to-and-fro scratchy or grating noise heard in systole, mid-diastole and presystole or in only 1 of these phases, with diagnosis made after confirmation by ≥2 cardiologists blinded to echocardiographic findings. Cardiac output, pulmonary capillary wedge and right atrial pressures were determined via the Swan-Ganz catheter at the time of admission. Total protein, albumin and globulin levels were measured on the day of admission. Colloid osmotic pressure was calculated according to the Nitta-Staub equations[6]: Colloid osmotic pressure = $a(2.8c + 0.18c^2 + 0.012c^3) + b(0.9c + 0.12c^2 + 0.004c^3)$, where a is albumin fraction, b is globulin fraction and c (g/dl) is total protein. Arterial blood was taken from the radial or femoral arteries at the time of admission, with the patients breathing room air. The alveolar arterial oxygen difference was calculated by assuming a respiratory quotient equal to 0.8.

Two-dimensional and M-mode echocardiography were performed with an SSD 870 phased-array sector scanner (Aloka, Tokyo). All classic views were recorded on videotape for subsequent analysis by observers unaware of the patients' clinical data. The presence of pericardial effusion was assessed on the third day of hospitalization with the method described by Horowitz et al.[7] An epicardial-pericardial separation that persisted throughout the cardiac cycle (D pattern) was considered diagnostic of pericardial effusion. Regional left ventricular wall motion abnormalities were assessed by 2-dimensional echocardiography obtained on the third day of hospitalization. Analysis of the left ventricular wall was performed with 11 segments obtained by long- and short-axis images,[8] and the number of segments with advanced asynergy (akinesia or dyskinesia) was calculated. Functional left ventricular aneurysmal motion was defined by 2-dimensional echocardiography as an area of thinned myocardium that was dyskinetic in systole, with distinct diastolic deformity and preserved adjacent wall motion.

Results are reported as mean ± standard deviation. Student's t *test was used for quantitative data, and chi-square analysis for qualitative data. Discriminant analysis was performed to evaluate the important variables affecting hospital mortality. The categorical variables were subdivided as being either absent or present. A p value <0.05 was considered statistically significant.*

Of the 330 patients with a Q-wave AMI, hydropericardia was observed in 45, and pericardial friction rub during the first 3 days after admission in 67. Hydropericardia and pericardial friction rub were absent in 218 patients. Hospital mortality rates were 27% in patients with hydropericardia, 12% in those with pericardial friction rub and 6% in those free of hydropericardia and pericardial friction rub. No patient had clinical or echocardiographic evidence of tamponade. There was a statistically significant difference in hospital mortality among the 3 groups ($p < 0.001$).

To determine the important variables associated with hospital mortality, 8 clinical variables were compared between survivors and nonsurvivors (Table I). When the presence of hydropericardia and pericardial friction rub were added to the 8 clinical variables in the multivariate analysis, age ($F = 7.6$, $p < 0.01$), alveolar arterial oxygen difference ($F = 12.0$, $p < 0.001$), advanced asynergic

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TABLE I Clinical Characteristics	Nonsurvivors (n = 34)	Survivors (n = 296)	p Value
Age (yr)	71 ± 10	60 ± 12	<0.001
Cardiac output (liters/min)	3.91 ± 1.06	4.99 ± 1.22	<0.001
Pulmonary capillary wedge pressure (mm Hg)	15 ± 6	11 ± 5	<0.001
Right atrial pressure (mm Hg)	6 ± 4	5 ± 3	NS
Alveolar arterial oxygen difference (torr)	48 ± 15	34 ± 12	<0.001
Colloid osmotic pressure (mm Hg)	23 ± 3	24 ± 4	NS
Aneurysmal motion			
Absent	25	248	NS
Present	9	48	
Asynergic segments	4.5 ± 1.4	2.8 ± 1.8	<0.001

NS = difference not significant.

segments ($F = 8.4$, $p < 0.01$) and hydropericardia ($F = 4.2$, $p < 0.05$) were found to be the statistically significant variables associated with hospital mortality. The probability of discrimination was 0.8.

Among the 45 patients with hydropericardia, 16 received intravenous or intracoronary urokinase, whereas 21 patients with pericardial friction rub and 66 patients free of hydropericardia and pericardial friction rub received urokinase. There was no significant difference in the number of the patients who received thrombolytic therapy among the 3 groups. We routinely give heparin to all patients with AMI in our coronary care unit. Similarly, no significant difference was seen among the 3 groups regarding the use of antiplatelet agents (aspirin) received by 35 patients with hydropericardia, 51 patients with pericardial friction rub and 163 patients free of hydropericardia and pericardial friction rub.

Among our 330 patients with a Q-wave AMI, a pericardial friction rub was present in 67 and hydropericardia in 45. In this study, pericardial friction rub and hydropericardia were evaluated with 8 other clinical variables to define their clinical significance in predicting hospital mortality. As a result of multivariate analysis, hydropericardia was selected with age, advanced asynergic segments and alveolar arterial oxygen difference as important variables associated with hospital mortality, but the relative importance of pericardial friction rub was low. The presence of pericardial effusion was not related to higher hospital mortality in a previous study,[3] but this might be because that study did not further evaluate the different mechanisms associated with the occurrence of pericardial effusion, i.e., inflammatory and hydrostatic effusion. As hydropericardia appears to result from an increase in the production of myocardial interstitial fluid or from interference with myocardial venous and lymph drainage,[9-11] an increase in hydrostatic pressure and disturbance of pulmonary gas exchange, resulting from more extensive myocardial damage, were primary factors related to increased mortality, and hydropericardia in itself was an important clinical sign related to hospital mortality.

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Impaired Hepatic Function Tests After Thrombolysis for Acute Myocardial Infarction

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During recent years, thrombolysis has become an established therapy for patients with an acute myocardial infarction (AMI). Some degree of impairment in hepatic function tests during AMI has been reported previously.[1] In addition, few reports documented transient toxic hepatitis in patients with peripheral vascular disease treated with streptokinase.[2,3] We prospectively studied the frequency of hepatic dysfunction in patients with AMI randomized to either streptokinase or recombinant tissue-type plasminogen activator (rt-PA).

One hundred eight consecutive patients in whom AMI was diagnosed entered the study. The diagnosis of AMI was based on typical, prolonged ischemic chest pain lasting from 30 minutes to 6 hours, ST-segment elevation of ≥0.1 mV in ≥2 contiguous leads on the admission electrocardiogram, and elevated serum creatine kinase levels of myocardial origin. Exclusion criteria were: age >75 years, cerebrovascular accident during the last 6 months, bleeding predisposition (i.e., oral anticoagulant therapy, recent trauma, history of bleeding), history of congestive heart failure or cardiac surgery, moderate to severe heart failure or cardiogenic shock on admission or dur-

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TABLE I Liver Function Tests on Admission, at Three Days and on Follow-Up at Three Months

	Streptokinase (n = 36) (FU = 27)	rt-PA (n = 41) (FU = 31)	Conservative (n = 32) (FU = 0)
		ALAT	
Admission	28 ± 13	28 ± 13	29 ± 11
Peak	90 ± 59 W4,M3	69 ± 38 W4,M2	43 ± 20 W3
Follow-up	27 ± 11	24 ± 9	—
		GGT	
Admission	26 ± 18	24 ± 17	24 ± 9
Peak	114 ± 147 W4,M2	36 ± 24 W3,NS	34 ± 24 W2
Follow-up	35 ± 26	26 ± 14	—
		AP	
Admission	93 ± 25	89 ± 26	96 ± 37
Peak	148 ± 95 W4,M1	96 ± 26 W1,NS	104 ± 40 W1
Follow-up	88 ± 22	80 ± 18	—
		BILI	
Admission	0.4 ± 0.3	0.4 ± 0.2	0.6 ± 0.3
Peak	0.8 ± 0.7 W4,NS	0.7 ± 0.3 W4,NS	0.8 ± 0.3 W3
Follow-up	0.5 ± 0.2	0.4 ± 0.1	—

W1 = p <0.05; W2 = p <0.01; W3 = p <0.001; W4 = p <0.0001 (peak value compared to admission value for each patient by the Wilcoxon test).
M1 = p <0.05; M2 = p <0.001; M3 = p <0.0001 (peak change in each group, compared to control group by the Mann-Whitney test).
ALAT = alanine aminotransferase (range 6 to 45 IU/ml); AP = alkaline phosphatase (range 10 to 85 IU/ml); BILI = bilirubin (range 0.1 to 1.1 mg/dl); FU = number of patients for whom follow-up data are available; GGT = gamma glutamyl transpeptidase (range <50 IU/ml); n = number of patients on admission; NS = difference not significant.

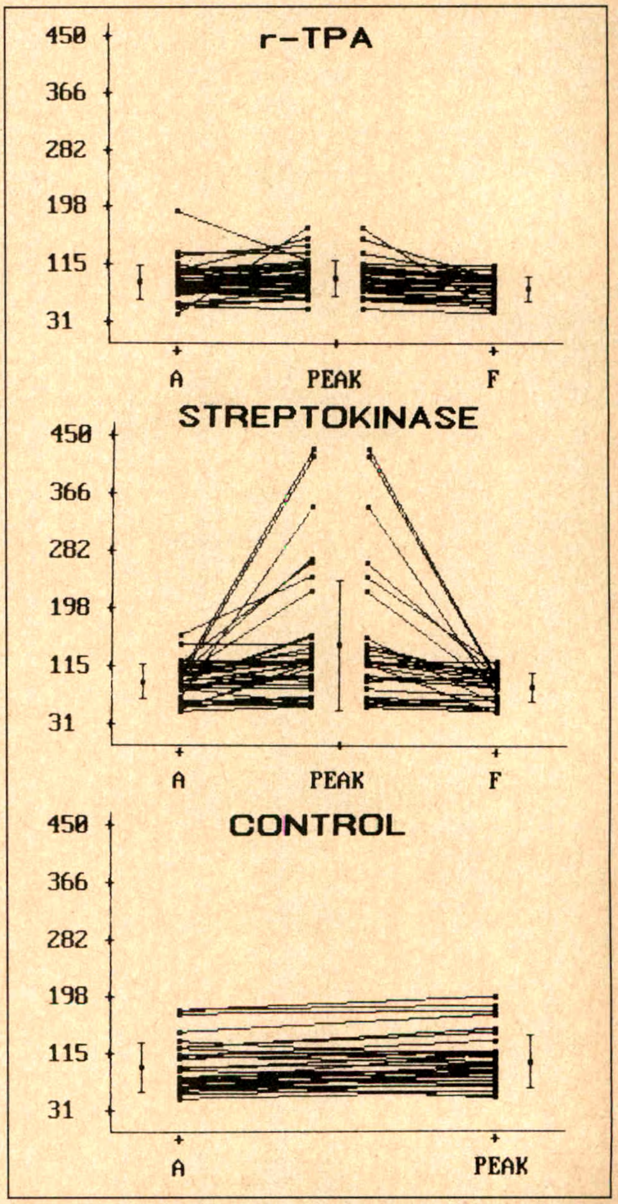

FIGURE 1. Alkaline phosphatase (IU/ml) level *(vertical axis)* in the 3 therapeutic groups (normal 10 to 85). *Vertical bars* represent the mean ± standard deviation. A = admission; F = follow-up level at 3 months; PEAK = peak level during hospitalization; r-TPA = recombinant tissue-type plasminogen activator.

ing hospitalization, and left bundle branch block on the qualifying entry electrocardiogram. Seventy-seven patients were randomly assigned to either 1,500,000 IU of streptokinase (Behring, Federal Republic of Germany) (n = 36) or 100 mg of rt-PA (Boehringer Ingelheim, Federal Republic of Germany) (n = 41). Thirty-two patients who did not consent to thrombolytic therapy or who were not suitable for such therapy served as control subjects. Liver function tests[2] were evaluated by measuring bilirubin, alkaline phosphatase, alanine aminotransferase and gamma glutamyl transpeptidase on admission and then at daily intervals for 5 days. The same blood tests were repeated on follow-up 3 months later.

Values within each group were compared by the Wilcoxon matched-pairs signed rank test (2-tailed test).[4] Changes among groups were compared with the Mann-Whitney test.[4] Values for each measurement are presented as the mean ± standard deviation.

Serum levels of alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase and bilirubin are listed in Table I. Admission values for all tests were normal in all 3 groups. At 3 days, all test results were significantly abnormal in all groups, compared with baseline values on admission. There was a slight liver function impairment in the control group, a moderate change in the rt-PA group and a pronounced change in the streptokinase group. Peak changes in liver function tests for the thrombolysis groups were compared with peak changes in values for the conservatively treated group. Levels of alkaline phosphatase, gamma glutamyl transpeptidase and alanine aminotransferase were significantly higher in the streptokinase group, whereas only alanine aminotransferase approached significantly higher levels in the rt-PA group. In the streptokinase group, 15 of 36 patients (41%) had elevated liver enzymes >2 times the normal level, compared with 11 of

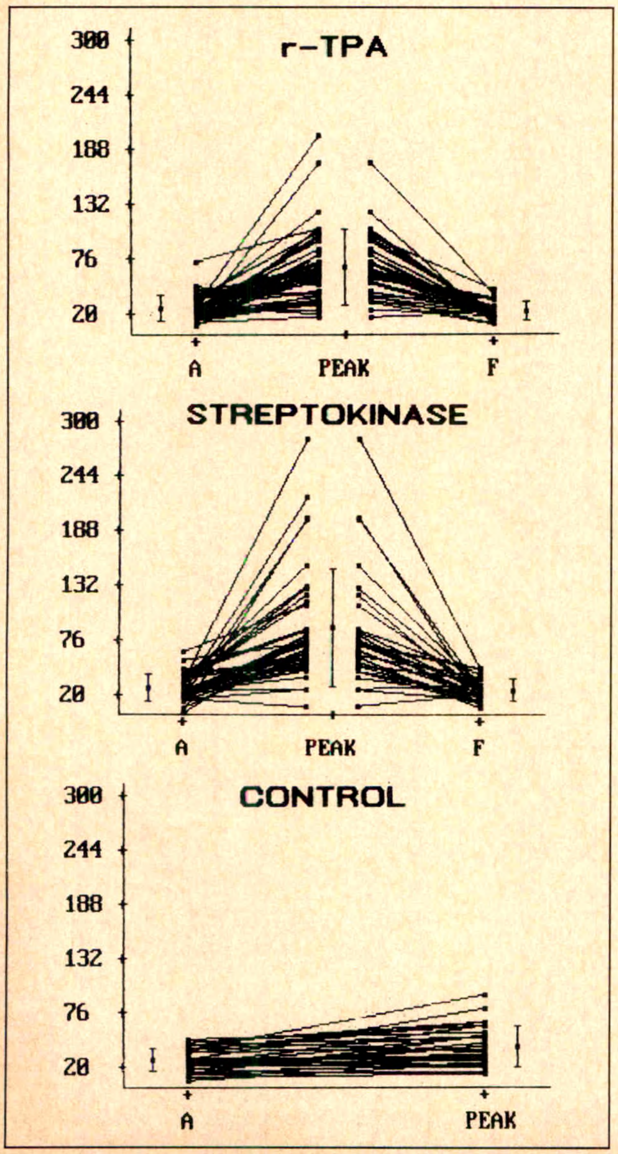

FIGURE 2. Alanine aminotransferase (IU/ml) level *(vertical axis)* in the 3 therapeutic groups (normal 6 to 45). *Vertical bars* represent the mean ± standard deviation. Abbreviations as in Figure 1.

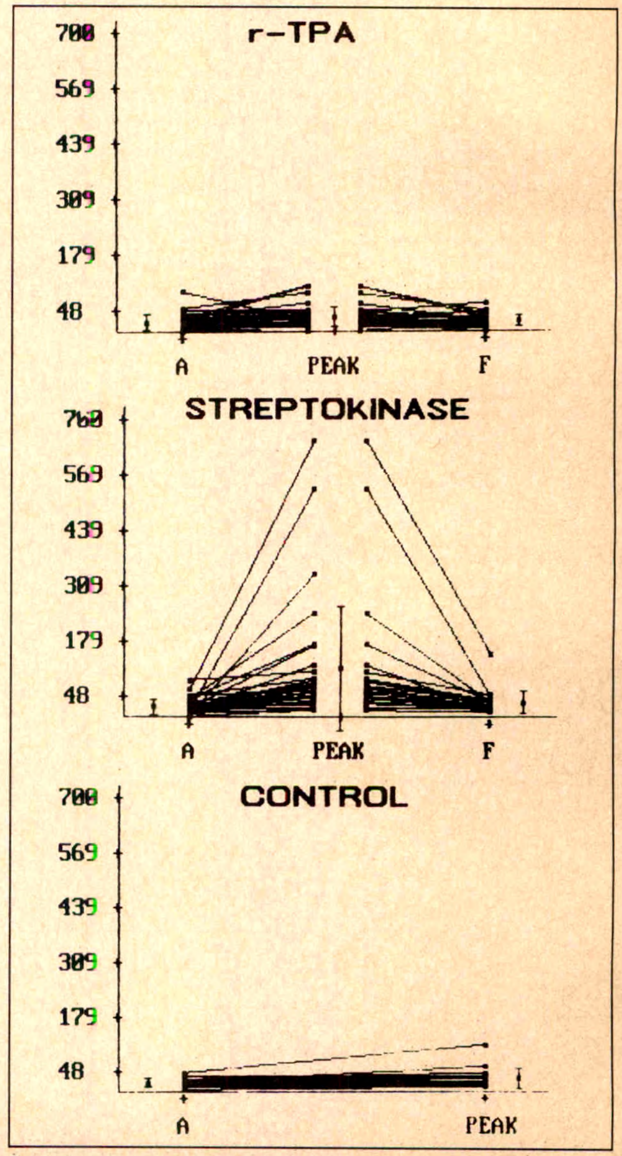

FIGURE 3. Gamma glutamyl transpeptidase (IU/ml) level *(vertical axis)* in the 3 therapeutic groups (normal <50). *Vertical bars* represent the mean ± standard deviation. Abbreviations as in Figure 1.

41 patients (27%) in the rt-PA group and 1 of 31 subjects (3%) in the control group. All these changes normalized at 3 months (Figures 1, 2 and 3).

A few case reports and a small study documented a degree of hepatic dysfunction after the administration of streptokinase to patients with peripheral arterial obstruction.[2,3,5] Mixed cholestatic and hepatocellular damage peaked at 3 days and then declined gradually within 2 months. We measured liver enzymes in patients with AMI and observed a similar trend. Some degree of hepatic dysfunction was found in those who did not receive thrombolytic therapy, a somewhat higher impairment in those treated with rt-PA and a pronounced change in those treated with streptokinase. No patient went into hepatic failure, and complete resolution was observed within 3 months.

The pathophysiologic mechanism of this toxic, hepatitis-like picture has not yet been elucidated. The 3 foremost possibilities are a sudden disturbance of the microcirculation of the liver, hepatotoxicity of the thrombolytic agent or the generated proteolytic enzymes, or an immunologic reaction. Some degree of liver function impairment during AMI without thrombolytic therapy has previously been described[1] and parallels our results. The infusion of streptokinase into an isolated hemoglobin-free and volume-constant perfused rat liver did not cause liver enzyme release, whereas the addition of plasmin or plasmin activator led to a marked acceleration of enzyme release.[2] Major adverse effects of streptokinase include bleeding, transient hypotension and a variety of allergic reactions.[6] It seems that the degree of liver function impairment that we observed was caused by the combined toxic effect of plasmin and plasmin activator, a component of allergic hepatitis and a reaction to hemodynamic derangement, all against a background of a mild basic liver function impairment known to occur in patients with an AMI. The greater prominence of liver dysfunction with streptokinase than with rt-PA may probably be ascribed to the more local action of rt-PA on formed thrombi.

We conclude that thrombolysis, particularly with streptokinase, causes an acute, pronounced impairment of hepatic function that does not lead to either acute hepatic failure or chronic hepatic disease and that heals gradually and completely within 3 months. We suggest that patients with impaired hepatic function who need thrombolytic therapy should be treated with rt-PA rather than with streptokinase.

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Influence of Gender on Inducibility of Ventricular Arrhythmias in Survivors of Cardiac Arrest with Coronary Artery Disease

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The influence of gender on the clinical manifestations, results of testing and prognosis of heart disease has recently been emphasized. These observations have included epidemiologic reports on different clinical predictors of sudden death in men and women[1] and disparate results of electrophysiologic testing in survivors of cardiac arrest.[2] Previous studies examining clinical predictors of arrhythmia inducibility in patients with cardiac arrest have documented that male gender is an important predictor of inducibility.[2] These studies enrolled patients with a variety of cardiac disorders and the difference in inducibility may have been partly explained by a differing prevalence of coronary artery disease.[2] This observation, however, could not fully explain the difference in outcome of electrophysiologic testing in men and women.[2] We undertook the present study to evaluate if differences in electrophysiologic substrate could explain the difference in inducibility between men and women with coronary artery disease and cardiac arrest.

We studied 52 men and 13 women with coronary artery disease and cardiac arrest unrelated to recent myocardial infarction and not associated with the administration of antiarrhythmic medications. The following variables were analyzed: age, history of myocardial infarction, ejection fraction, and number of diseased coronary arteries (defined as ≥70% obstruction), inducibility of sustained ventricular arrhythmias, endocardial catheter mapping abnormalities, and signal-averaged electrocardiography. Our stimulation protocol,[3] endocardial catheter mapping scheme[4] and methods of signal-averaged electrocardiography[5] have been described

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This report was supported in part by Grant HL28093 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Dr. Josephson is the Robinette Foundation Professor of Medicine in Cardiology. Manuscript received August 15, 1990; revised manuscript received and accepted November 13, 1990.

TABLE I Clinical Variables and Results of Endocardial Mapping and Signal-Averaged Electrocardiography in Male and Female Survivors of Cardiac Arrest

	Men	Women	p Value
Number of patients	52	13	
Age (yr)	60 ± 8	65 ± 7	0.04
History of MI (%)	42 (81)	10 (77)	NS
Number of diseased coronaries	2.3 ± 0.8	1.9 ± 0.9	NS
Ejection fraction (%)	37 ± 17	31 ± 22	NS
Inducible arrhythmias (%)			
VT	27 (52)	4 (31)	
VF	11 (21)	1 (8)	
NSVT	7 (13)	5 (38)	
None	7 (13)	3 (23)	
Normal sites (%)	55 ± 27	51 ± 28	NS
Abnormal sites (%)	42 ± 26	43 ± 25	NS
Fractionated sites (%)	3 ± 8	6 ± 15	NS
Early sites (%)	15 ± 15	16 ± 17	NS
Late sites (%)	7 ± 10	8 ± 12	NS
Late, abnormal or fractionated sites (%)	5 ± 9	9 ± 13	NS
Duration of longest electrogram (ms)	107 ± 33	107 ± 22	NS
Total endocardial activation time (ms)	60 ± 32	55 ± 16	NS
Offset latest electrogram	115 ± 36	118 ± 31	NS
Filtered QRS duration (ms)	122 ± 30	108 ± 24	NS
Root-mean-square voltage last 40 ms (μV)	34 ± 30	42 ± 21	NS
Abnormal SAECG	64%	43%	NS

MI = myocardial infarction; NS = difference not significant; NSVT = nonsustained ventricular tachycardia; SAECG = signal-averaged electrocardiogram; VF = ventricular fibrillation; VT = ventricular tachycardia.

in detail previously. Stimulation includes the introduction of 1, 2 and 3 extrastimuli at 2 right ventricular sites at ≥2 drive cycle lengths and rapid ventricular pacing. Nonsustained ventricular tachycardia was not an end point for stopping the electrophysiologic study, and all patients underwent stimulation to refractoriness or induction of hemodynamically compromising sustained ventricular arrhythmia. Patients with bundle branch block (7 men and 4 women) were excluded from signal-averaged electrocardiography. Signal-averaged electrocardiographic data were available for 42 men and 7 women without bundle branch block; catheter mapping data were complete for all patients. Of the patients included for signal-averaged electrocardiography, 71% of the men and 43% of the women were inducible.

Endocardial electrograms were classified as normal, abnormal or fractionated according to previously described criteria.[4] Total endocardial activation time was defined as time from activation of the earliest to activation of the latest electrogram. Early and late sites were defined as sites exhibiting activity preceding or after the surface QRS, respectively. The signal-averaged electrocardiograms were compared for filtered QRS duration and root-mean-square voltage of the terminal 40 ms. Duration >110 ms or voltage of the terminal 40 ms <25 μV was considered abnormal.

Sustained ventricular tachycardia was defined as uniform tachycardia lasting ≥30 seconds or requiring cardioversion. Nonsustained ventricular tachycardia was defined as uniform tachycardia lasting ≥3 beats and <30 seconds and not requiring cardioversion. Ventricular fibrillation was defined as polymorphic tachycardia with no discrete QRS.

Statistical analysis first included univariate regression analysis to identify those clinical and electrophysiologic variables with at least a marginal ($p < 0.1$) relation to inducibility. These variables were then entered in a multivariate regression analysis with inducibility as the dependent variable. Chi-square analysis and analysis of variance were used to examine differences between men and women as indicated. Statistical significance was defined as $p < 0.05$ for all analyses.

Table I presents the clinical characteristics and results of endocardial mapping and signal-averaged electrocardiography of male and female patients.

On multivariate analysis, male gender was the variable most strongly associated with inducibility ($p < 0.001$). The percentage of fractionated sites ($p < 0.01$) and ejection fraction ($p < 0.05$) were also significantly related to inducibility. Men were approximately twice as likely to have sustained ventricular arrhythmias induced than women (73 vs 39%, $p = 0.01$). The men and women with inducible ventricular tachycardia required a similar number of extrastimuli to be induced (2.3 ± 0.7 for men and 2.3 ± 0.5 for women). In contrast, men induced to ventricular fibrillation required 2.8 ± 0.6 extrastimuli ($p < 0.05$ vs men with induced ventricular tachycardia).

The men were more frequently inducible, the women were older, but otherwise the 2 groups did not differ with respect to any clinical, endocardial mapping, or signal-averaged electrocardiographic variable (Table I).

Our study corroborated the observations of previous investigators[2] that among patients with cardiac arrest, women are less likely to have inducible ventricular tachycardia or ventricular fibrillation. In contrast to the previous studies that enrolled patients with a variety of cardiac diagnoses, we limited our study population to patients with coronary artery disease. The electrophysiologic substrate of cardiomyopathy is different and less well-defined than that of coronary artery disease and therefore it is important to define the population precisely at study. Part of the difference in inducibility in the earlier studies may be explained by differences in underlying cardiac diagnoses.[2] However, in our study limited to patients with coronary artery disease, this difference based on gender is still present. Furthermore, there was no difference between men and women in ejection fraction, number of diseased coronary arteries, or history of myocardial infarction to account for the difference in inducibility.

We also could not demonstrate any significant difference between men and women in the extent of electrophysiologic substrate. None of the catheter mapping or signal-averaged electrocardiographic indexes differed between the 2 groups. Catheter mapping may be subject to a sampling error in that small areas of abnormalities may be missed, but previous reports from our laboratory have established that catheter mapping is reliable in identifying abnormal substrate in patients with inducible arrhythmias.[4]

The reason for the difference in inducibility between men and women is therefore unknown. The poorer prognosis for women undergoing bypass surgery has been

attributed to a referral bias, whereby women are referred for surgery later in the course of their illness when their functional class has deteriorated.[6] This may be based on a fallacious perception that women are less likely to benefit from interventions in coronary artery disease. It would be difficult to conceive of a selection bias operating in the referral of cardiac arrest patients for electrophysiologic studies. Furthermore, if a referral bias similar to that for bypass surgery was in existence, one would expect women referred for electrophysiologic study to have more severe disease and perhaps have inducible ventricular tachycardia or ventricular fibrillation more frequently than men, the opposite of our current results.

We examined differences in substrate between men and women, but other factors may be important in modulating the propensity to tachyarrhythmias that we did not address, such as the role of the autonomic nervous system, the presence or absence of ischemia, or transient electrolyte imbalances.

The finding of less frequent inducibility of ventricular tachycardia or ventricular fibrillation in female survivors of cardiac arrest is not explained by differences in electrophysiologic substrate, emphasizing our imperfect understanding of the pathophysiology of sudden death and calling into question the validity of applying a uniform strategy of management for both men and women with cardiac arrest.

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Frequency of Late Potentials in Systemic Sclerosis

Debra K. Moser, MN, RN, William G. Stevenson, MD, Mary A. Woo, MN, RN, Steven R. Weiner, MD, Philip J. Clements, MD, Sharon M. Suzuki, RN, Connie L. Wright, RN, John S. Child, MD, Janine Krivokapich, MD, and Antoine Alhajje, MD

In some patients with coronary artery disease, myocardial scar produces areas of delayed myocardial activation. Low amplitude, high-frequency electrograms can be recorded from such areas. It is likely that these areas of scar are the substrate for reentrant ventricular arrhythmias.[1] The signal-averaged electrocardiogram detects this low-amplitude, high-frequency electrical activity known as late potentials.[2] We hypothesized that myocardial scarring in systemic sclerosis could produce areas of delayed myocardial activation detectable by the signal-averaged electrocardiogram. This study describes the frequency of late potentials in patients with systemic sclerosis.

After approval of the protocol by the appropriate Human Subject Protection Committee, 88 consecutive patients who satisfied American Rheumatism Association criteria for systemic sclerosis were recruited from scleroderma clinics at 2 metropolitan area hospitals. Patients were excluded if they had a history of atherosclerotic coronary artery disease, angina pectoris, myocardial infarction, sustained ventricular tachycardia or cardiac arrest. Twelve patients were taking nifedipine for Raynaud's phenomenon and 4 patients were taking enalapril for hypertension. One patient was taking mexiletine and 1 was taking quinidine for ventricular ectopic activity at the time of signal-averaged electrocardiography.

Forty-six normal subjects who had no evidence of cardiac disease by history, physical examination and 12-lead electrocardiogram, and no history of diabetes, hypertension or family history of early cardiac death were studied as control subjects. No control subject was receiving medication and all women were premenopausal.

Signal-averaged electrocardiograms were obtained using bipolar orthogonal XYZ leads acquired at a 2,000-Hz sampling frequency with 12-bit resolution for analog-to-digital conversion (Corazonix Corporation, Oklahoma City, Oklahoma). Noisy or abnormal complexes were rejected by a template recognition algorithm. Complexes were collected until a noise level of 0.30 μV was reached. The signal-averaged QRS vector magnitude was bidirectionally high-pass filtered at 25 Hz. The end of the vector QRS complex was determined by computer algorithm as the point at which the mean voltage was 3 times the noise level. The following filtered QRS vector complex indexes were measured by an automated algorithm: (1) QRS duration, (2) root-mean-square voltage of the terminal 40 ms, and (3) duration of the low-amplitude (<40 μV) signals in the terminal QRS. Normal values were: (1) QRS duration <110 ms, (2) root-mean-square voltage >25 μV, and (3) low-amplitude signal duration <38 ms. A late potential was defined as the presence of a prolonged QRS duration plus either a low root-mean-square voltage or a prolonged low-amplitude signal duration. To determine reproducibility, the signal-averaged electrocardiogram was repeated after 5 ± 2 months in 26 patients.

Within 1 month of the signal-averaged electrocardiogram, we prospectively obtained 24-hour ambulatory electrocardiograms in 46 patients and Doppler, M-mode and 2-dimensional echocardiograms in 47 patients. Logistic considerations prevented obtaining these studies in the remaining patients within 1 month of the signal-averaged electrocardiogram.

Categorical data were analyzed using Fisher's exact test. Student's t *tests were used for continuous data, presented as mean ± standard deviation. Reproducibility of signal-averaged electrocardiogram findings was assessed by linear regression.*

There were no differences between patients with systemic sclerosis and control subjects by gender, but patients with systemic sclerosis were significantly older than control subjects (Table I). Mean duration of symptoms of systemic sclerosis was 8 ± 8 years (range 0.5 to 34).

Twenty-six percent of patients with systemic sclerosis had at least 1 abnormal signal-averaged electrocardiogram parameter (Table I). However, 22% of the normal control subjects also had at least 1 such parameter (Table I). Patients and control subjects did not differ in the incidence of individual signal-averaged electrocardio-

TABLE I Comparison of Patients with Sytemic Sclerosis and Control Subjects

	SS Patients	Control Subjects	p Value
Number of patients	88	46	
Mean age (yr)	53 ± 13	33 ± 7	0.01
Women (%)	73 (83)	38 (83)	0.96
SAE parameters			
Abnormal QRS + RMS or LAS (%)	8 (9)	0 (0)	0.03
QRS ≥110 ms (%)	14 (16)	5 (11)	0.42
RMS ≤25 μV (%)	17 (19)	5 (11)	0.16
LAS ≥38 ms (%)	9 (10)	3 (7)	0.35
Any 1 abnormal parameter (%)	23 (26)	10 (22)	0.36

LAS = low-amplitude signal duration <40 μV; QRS = QRS duration of filtered QRS complex; RMS = root-mean-square voltage of the last 40 ms of filtered QRS; SAE = signal-averaged electrocardiogram; SS = systemic sclerosis.

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graphic abnormalities, reflecting the relatively high number of false-positive results in the control subjects when only individual signal-averaged electrocardiographic parameters are considered (Table I). However, no control subject had an abnormal QRS duration plus an abnormal root-mean-square voltage or low-amplitude signal duration, whereas 9% of patients with systemic sclerosis had this combination ($p = 0.03$; Figure 1). Both patients taking antiarrhythmic agents had normal signal-averaged electrocardiograms.

A second signal-averaged electrocardiogram was obtained 5 ± 2 months after the initial study in 26 patients with systemic sclerosis. The correlation coefficient was 0.95 for QRS duration (Figure 2), 0.89 for root-mean-square voltage and 0.85 for low-amplitude signal duration. Only 2 individual parameters in 2 separate subjects changed to a clinically relevant degree. In 1 subject, an abnormal root-mean-square voltage became normal and, in another subject, a normal low-amplitude signal duration became abnormal. No subject had a clinically

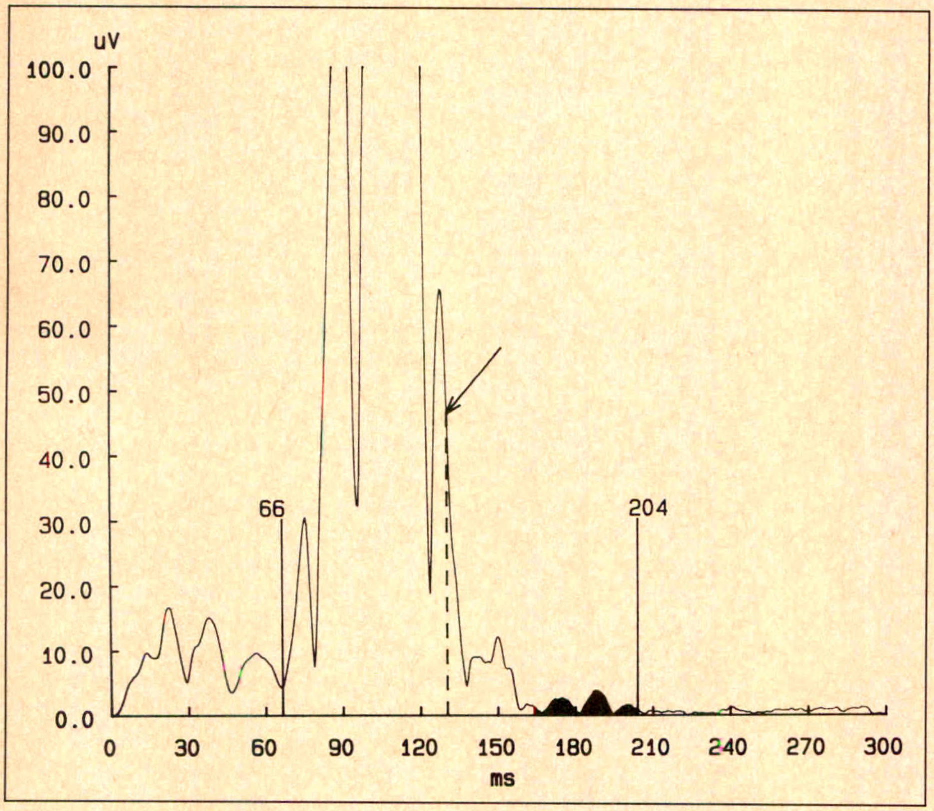

FIGURE 1. Abnormal signal-averaged electrocardiogram from a 38-year-old woman with systemic sclerosis. The onset and end of the QRS are marked with *vertical lines*. The QRS duration is prolonged to 139 ms. A low-amplitude component is visible in the terminal portion of the QRS complex *(shaded area)*. The terminal QRS root-mean-square voltage was 1.93 μV and the low-amplitude signal duration was 74 ms.

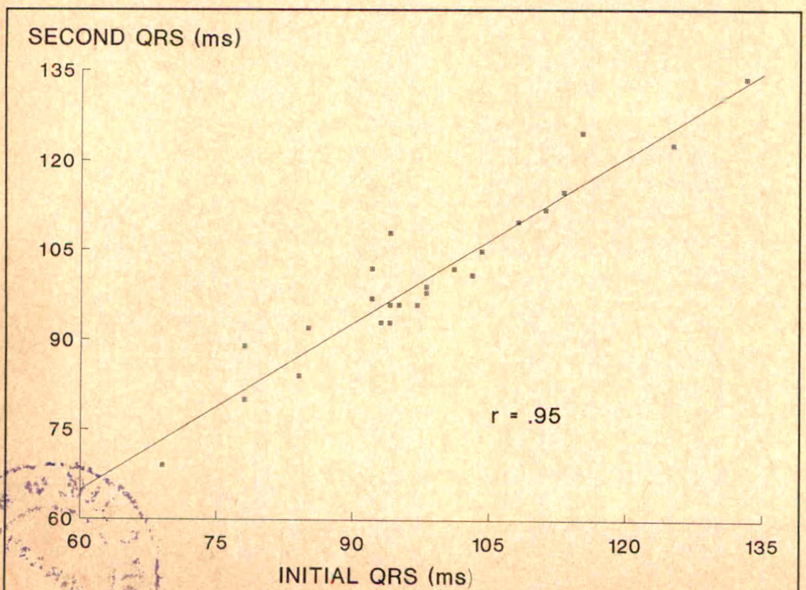

FIGURE 2. Scatterplot of initial versus subsequent QRS duration measurements. The correlation coefficient was 0.95, p <0.001.

important change in the QRS duration. When abnormal QRS duration plus root-mean-square voltage or low-amplitude signal duration was used to define late potentials, reproducibility was 100%.

Complex or frequent ventricular ectopic activity occurred in 3 of 5 patients (60%) with an abnormal signal-averaged electrocardiogram versus 11 of 41 or 27% with a normal signal-averaged electrocardiogram ($p = 0.16$). Echocardiography detected an area of left ventricular hypokinesia or akinesia in 4 of 5 patients (80%) with an abnormal signal-averaged electrocardiogram versus 3 of 42 patients (7%) with a normal signal-averaged electrocardiogram ($p < 0.01$).

Cardiac involvement in systemic sclerosis is common and can exist without accompanying signs and symptoms.[3–5] By the time it becomes clinically apparent, the prognosis is poor.[6] Several methods for detecting early cardiac involvement in systemic sclerosis have been evaluated. Isometric exercise during echocardiography,[5] 12-lead electrocardiography and echocardiography during rest or exercise,[4,7–8] exercise myocardial thallium scanning, rest and exercise radionuclide ventriculography[3] and 24-hour continuous electrocardiography[9] may uncover subclinical myocardial involvement in systemic sclerosis. Currently, only 12-lead electrocardiography, echocardiography and 24-hour ambulatory electrocardiography are used frequently and all have limitations. A simple, noninvasive technique for defining systemic sclerosis cardiac disease would be of value. Our study demonstrates that systemic sclerosis can cause late potentials that are reproducibly detectable on the signal-averaged electrocardiogram. A possible cause of these late potentials may be myocardial fibrosis, which is thought to be produced by microvascular vasospasm.[10] Myocardial fibrosis has been associated with late potentials in patients with ventricular tachycardia even in the absence of myocardial infarction.[11] Although we do not have morphologic confirmation of myocardial fibrosis in our patients, the association of late potentials with abnormal left ventricular wall motion is consistent with this hypothesis.

Criteria for defining late potentials vary. Some investigators have required only 1 parameter among QRS duration, root-mean-square voltage and low-amplitude signal duration to be abnormal.[12] Others have required 2 or 3 parameters to be abnormal.[13,14] Simson[15] reported that definitions of late potentials that included the QRS duration were more accurate than those that used only voltage measurements. Although the use of a single abnormal parameter to define late potentials may be sensitive, specificity is low and the use of ≥ 2 abnormal parameters improves specificity and the predictive value of the signal-averaged electrocardiogram.[12] Our results are in agreement with these studies. Abnormal individual signal-averaged electrocardiographic parameters were found in up to 26% of patients with systemic sclerosis and in up to 22% of control subjects. The combination of prolonged QRS duration plus either an abnormal low-amplitude signal duration or root-mean-square voltage differentiated patients with systemic sclerosis from normal control subjects. Furthermore, this combination was associated with abnormal left ventricular wall motion.

Although 60% of patients with systemic sclerosis and late potentials had complex ventricular ectopic activity, 78% of patients with complex or frequent ectopic activity had normal signal-averaged electrocardiograms. Complex or frequent ventricular ectopic activity can occur in normal subjects and it is possible that in some patients ectopic activity was unrelated to systemic sclerosis cardiac involvement. However, complex ventricular arrhythmias are associated with an increased risk of mortality in systemic sclerosis.[6] Thus, the signal-averaged electrocardiogram is not an adequate screening tool for identifying patients with systemic sclerosis and complex ventricular arrhythmias. Whether late potentials identify patients who will have cardiac complications and mortality from systemic sclerosis is unknown.

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Effect of Balloon Aortic Valvuloplasty on Doppler Indexes of Left Ventricular Diastolic Filling

Warren J. Manning, MD, Marilyn F. Riley, BS, and Patricia C. Come, MD

Left ventricular (LV) hypertrophy, developing in response to chronic pressure overload, serves to normalize systolic wall stress and preserve systolic function.[1] However, this occurs at the expense of an impairment of LV isovolumic relaxation and early diastolic filling.[2] Increases in LV afterload have also been thought to cause acute impairment in ventricular relaxation. This study sought to determine whether percutaneous balloon aortic valvuloplasty, by reducing afterload in patients with LV hypertrophy due to aortic stenosis, would result in an early favorable effect on Doppler echocardiographic indexes of ventricular filling.

The study population consisted of 190 consecutive patients undergoing balloon aortic valvuloplasty at the Beth Israel Hospital between December 28, 1985 and August 10, 1988. Of these, 163 patients were excluded from analysis owing to coexisting conditions associated with abnormal patterns of LV diastolic filling: prior myocardial infarction or significant coronary artery disease, defined as >50% diameter narrowing of a major epicardial vessel; greater than trivial mitral or aortic regurgitation identified by Doppler echocardiographic examination; concurrent mitral stenosis; or non-sinus rhythm (atrial fibrillation/flutter, ventricular paced rhythm or frequent ventricular ectopic activity). Eight additional patients either did not undergo or had inadequate transmitral Doppler studies before and after valvuloplasty. The remaining 19 patients included 10 men and 9 women (mean age ± standard deviation 75 ± 14 years). Echocardiographic and radionuclide scintigraphy were performed in patients 24 to 72 hours before and 48 to 72 hours after balloon aortic valvuloplasty. Informed consent was obtained from all patients, and the study protocol was approved by the Investigational Review Board of the Beth Israel Hospital, Boston, Massachusetts.

Two-dimensional, M-mode and pulsed Doppler echocardiograms were obtained with an Advanced Technology Labs, Inc. model MK600 combined imaging, M-mode and Doppler echocardiograph equipped with a 3.0-MHz mechanical transducer. M-mode data were recorded of the LV septum and posterior wall immediately below the mitral valve leaflets from a parasternal long-axis view. LV mass was calculated by the modified formula of Devereaux et al[3] and normalized for body surface area (m^2). Pulsed Doppler transmitral inflow velocities were recorded from the apical 4-chamber view, with the sample volume positioned between the tips of the mitral leaflets. Hard copy recordings of the M-mode and Doppler spectra were recorded at a paper speed of 100 mm/s. All recordings were obtained during quiet respiration in the left lateral position. Continuous-wave Doppler recordings of the aortic jet velocity were obtained using a Vingmed SD-100 Doppler unit with transducer placement at the apical and right parasternal windows.

Transmitral Doppler signals were digitized with the use of a graphics tablet (Summagraphics) and microcomputer (IBM AT) with custom-written software (Datastat). Digitization consisted of manual tracing of the velocity curves. Peak velocities of the early filling (E) wave and atrial filling (A) wave were determined.[4] The velocity-time integrals of the E and A waves were then obtained by integrating the flow velocity profiles at 4-ms intervals. Percent atrial systolic contribution (percent A wave) to total LV filling was assessed by dividing the area under the A wave by the total area under the diastolic velocity-time curve. Percent filling during the first one-third of diastole was calculated as percent of the diastolic time-velocity integral occurring during the first one-third of diastole. Time for 50% LV filling was calculated as the time required to attain 50% of the total time-velocity integral. For all Doppler measurements, values reported represent the mean of measurements obtained from 3 to 5 cardiac cycles.

Gated radionuclide angiograms were performed after injection of red blood cells labeled with 20 mCi of technetium-99m by the in vitro technique, as previously described.[5]

Cardiac catheterization and valvuloplasty were performed using a retrograde femoral arterial approach and single balloon technique, as previously described.[5]

Pulsed Doppler echocardiograms were also recorded in 12 control subjects (9 men, 3 women; mean age 69 years, range 62 to 76) without cardiac abnormalities as assessed by history, physical examination or echocardiography. Control subjects also underwent radionuclide scintigraphy at rest for assessment of LV ejection fraction.

All data are expressed as mean ± standard deviation. Statistical significance of changes in Doppler parameters was assessed using Student's paired t *test. Data for patients and control subjects were compared with Student's unpaired* t *test.*

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TABLE I Group Mean (± SD) Echocardiographic and Radionuclide Data

	Control	AS (Before BAV)	AS (After BAV)
No. of patients	12	19	19
Heart rate (beats/min)	56 ± 7	66 ± 8*	69 ± 8*
Peak A velocity (m/sec)	0.63 ± 0.14	0.99 ± 0.35*	1.00 ± 0.33*
Peak E velocity (m/sec)	0.52 ± 0.17	0.68 ± 0.18	0.68 ± 0.22
Peak E/A velocity	0.84 ± 0.23	0.83 ± 0.71	0.80 ± 0.71
Percent A-wave filling	39 ± 8	39 ± 8	40 ± 10
Time for 50% LV filling (ms)	263 ± 81	226 ± 45	220 ± 42
Percent filling first one-third diastole	45 ± 8	37 ± 11	36 ± 9
LV wall thickness (mm)	10 ± 2	18 ± 3†	
Radionuclide LVEF	0.73 ± 0.04	0.72 ± 0.15	0.69 ± 0.10

* $p < 0.05$ AS vs control; † $p < 0.001$ AS vs control.
A = atrial filling; AS = aortic stenosis; BAV = balloon aortic valvuloplasty; E = early filling; LV = left ventricular; LVEF = left ventricular ejection fraction; SD = standard deviation.

Clinical and echocardiographic characteristics of the patients with aortic stenosis and of the controls are summarized in Table I. Initial echocardiograms revealed symmetric LV hypertrophy in all patients with aortic stenosis, with a calculated LV mass index of 179 ± 45 g/m² ($p < 0.001$ vs control group). Radionuclide LV ejection fraction was similar in patients and controls. Compared with the control group, transmitral Doppler indexes before valvuloplasty in patients with aortic stenosis differed only in peak A-wave velocity. There were no significant differences in any of the other Doppler indexes studied. Furthermore, there were no significant correlations between any of the Doppler parameters and LV systolic pressure in the patients with aortic stenosis. Heart rate at rest was slightly higher in the group with aortic stenosis compared with the control subjects.

After balloon dilation, there were significant decreases in LV systolic pressure and mean transaortic pressure gradient measured by both catheterization and continuous-wave Doppler. There were no significant changes in either LV end-diastolic pressure, heart rate or resting radionuclide LV ejection fraction. There were also no significant changes in any of the Doppler parameters examined (Table I). Analysis of the subgroup of 12 patients in whom heart rate at both echocardiographic studies varied by <10% was similar. Furthermore, there was no association between changes in the Doppler indexes examined and changes in LV systolic pressure or transaortic pressure gradients.

The purpose of this study was to examine the early effects of balloon aortic valvuloplasty on Doppler indexes of LV filling. Doppler techniques were chosen for analysis, because transmitral Doppler velocity profiles have been shown to reliably characterize patterns of LV filling.[4] To minimize potential confounding effects of afterload-induced changes in myocardial ischemia or regurgitation on Doppler parameters of LV filling,[6,7] patients with more than trivial mitral or aortic regurgitation, or with significant epicardial coronary stenoses were excluded. A large percentage (86% in this study) of adult patients undergoing balloon aortic valvuloplasty have these coexisting conditions.[8]

At baseline, the patients with aortic stenosis had an increase in peak A-wave velocity compared with that in controls. These findings are similar to those of Otto et al[9] in patients with aortic stenosis and concomitant LV hypertrophy. After aortic valvuloplasty, and despite significant declines in both LV systolic pressure and transaortic pressure gradient, there were no significant changes in any of the transmitral Doppler indexes examined. This observation is consistent with previous invasive hemodynamic findings. Paulus et al[10] found no change in the time constant of LV pressure decay after either balloon aortic valvuloplasty or intravenous nitroprusside in patients with aortic stenosis. Their study population was similar to ours in that no patient had significant mitral regurgitation, coronary artery disease, or more than trivial aortic insufficiency. Takenaka et al[11] examined transmitral Doppler indexes of LV filling after an acute increase in systolic aortic blood pressure induced by intravenous infusion of phenylephrine. Despite a 30% increase in systolic arterial pressure, there were no changes in peak E-wave or peak A-wave velocities, or isovolumic relaxation time. Although their patients did not have LV hypertrophy, the available invasive and noninvasive hemodynamic data cited are consistent with the findings in this study, that early LV diastolic filling is not altered acutely by a significant reduction in LV systolic pressure. Our findings are in contrast to those published by Stoddard et al,[8] in which increases were noted in peak E velocity and peak E/A ratios after successful balloon aortic valvuloplasty in the subgroup of patients without mitral regurgitation, despite a similar change in mean gradient to that noted in our patient population. These differences could be explained by the different patient populations studied. In Stoddard's study, almost 40% of the valvuloplasty group had significant coronary artery disease, and 64% had significant mitral regurgitation. Controlling for mitral regurgitation and ischemia is important because the severity of mitral regurgitation has been shown to decrease significantly after percutaneous balloon aortic valvuloplasty.[12]

There are several limitations to this study. By excluding those with coexisting mitral or aortic regurgitation, coronary disease and abnormal LV systolic function, a relatively small number of patients were available for study. Our population, however, represents the largest homogeneous group examined in this manner. Hemodynamic and echocardiographic data were not obtained simultaneously, and preload was not assessed at the time of the echocardiographic studies. The lack of a change in

filling indexes may also be related to significant residual aortic stenosis. Our data do not preclude the possibility that changes in Doppler indexes of LV filling might be observed later, particularly if there was regression of LV hypertrophy. Finally, although the patients studied did not have significant epicardial coronary artery disease, myocardial ischemia may have been present, caused by a relative decrease in coronary blood flow, or to hypotension induced by balloon inflation. None of the patients, however, had electrocardiographic or serum creatine phosphokinase evidence of myocardial injury.

Thus, percutaneous balloon aortic valvuloplasty in patients with aortic stenosis, concentric LV hypertrophy and preserved systolic function is not associated with early changes in transmitral Doppler inflow indexes of LV filling.

Acknowledgment: We are grateful for the assistance of James J. Ferguson III, MD, for developing a computer program for analysis of the Doppler recordings.

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A Doppler Echocardiographic Examination of the Normal Aortic Valve and Left Ventricular Outflow Tract

William R. Davidson, Jr., MD, Michael J. Pasquale, MD, and Claude Fanelli, MD

Since first reported,[1] the continuity equation has become an accepted clinical tool for the calculation of mean aortic valve area.[1-3] In subjects without aortic disease, 2-dimensional echocardiography has been used to measure the midsystolic or maximal aortic valve area.[4] No studies have calculated the mean area of normal aortic valves using the continuity equation. We studied the left ventricular (LV) outflow tract and aortic valve to establish normal values for the measurements employed in the continuity equation and to relate aortic valve area to LV outflow tract dimensions, body surface area and stroke volume.

Subjects were recruited from clinical patients seen in the echocardiographic laboratory and had no cardiac disease by history or physical examination. All subjects had a normal echocardiogram, a structurally normal-appearing aortic valve and no aortic insufficiency by Doppler interrogation.

The LV outflow tract diameter was measured from a parasternal long-axis view. The transducer was swept across the outflow tract to find the widest diameter, where the outflow tract endocardium was most sharp and distinct. To measure the diameter, cursors were placed on the endocardial line of the anterior and posterior outflow tract at the base of the anterior mitral valve leaflet, parallel to the plane of the aortic anulus, perpendicular to the outflow tract and 1 to 2 mm proximal to the aortic anulus (the site of aortic leaflet insertion). The walls of the outflow tract are usually parallel at this site.

Aortic velocities were recorded with a 2.0-MHz, continuous-wave Doppler transducer in an attempt to obtain the fastest spectral envelopes possible. Usually, an apical view provided the best wave forms, although the suprasternal or other views were sometimes superior. From an apical long-axis or 4-chamber view, the pulsed Doppler sample volume was placed at the level of the measured diameter of the outflow tract. Wave forms typically appear parabolic here, with little variance around the mean. Spectral broadening was seen if the sample volume entered the aortic anulus, at which time the sample volume was repositioned to a slightly more proximal site. All measurements were made in triplicate. A Hewlett-Packard AC77020 or an Interspec XL-3 was used, with imaging and pulsed Doppler frequencies of 2.5 to 3.5 MHz.

Outflow tract area was calculated from the diameter as $\pi(D/2)^2$. Doppler wave forms were measured with the internal analytic capabilities of the imaging systems for peak velocity, systolic ejection period and the time-velocity integral. Stroke volume was calculated as outflow tract area × outflow tract time-velocity integral and multiplied by heart rate to obtain cardiac output. Aortic valve area was calculated as stroke volume divided by aortic valve time-velocity integral.

To determine the influence of changing stroke volume on aortic valve area, 10 subjects with Swan-Ganz catheters placed for clinical indications underwent repeat examinations on 2 separate days ($n = 6$) or before and after sublingual administration of 0.4 mg of nitroglycerin on the same day ($n = 4$). Thermodilution cardiac outputs were obtained simultaneously with Doppler examinations. Subjects gave informed consent for nonclinical studies and the administration of nitroglycerin. Thermodilution cardiac outputs were calculated from the mean of 3 measurements varying by ≤10%. Echocardiographic and Doppler measurements were obtained by investigators blinded to thermodilution data. Linear regression was used to compare echocardiographic and Doppler measurements with body surface area and Doppler stroke volume and to compare the change in valve area and other echocardiographic variables with the change in thermodilution stroke volume.

Forty-one subjects with no cardiac disease were studied (30 men, 11 women). Results, given as mean ± standard deviation, are listed in Table I. Aortic valve area ranged from 1.9 to 4.1 cm² and outflow tract area from 2.4 to 5.3 cm². Intraobserver outflow tract diameters

TABLE I Doppler and Echocardiographic Measurements of the Aortic Valve and Outflow Tract in Normal Subjects

Age (yr)	33 ± 12
Male/female	30/11
BSA (m²)	1.86 ± 0.21
Heart rate (beats/min)	63 ± 11
Left ventricular outflow tract	
Peak velocity (m/s)	0.98 ± 0.18
TVI (cm)	20.6 ± 3.3
Diameter (cm)	2.2 ± 0.2
Diameter index (cm/m²)	1.2 ± 0.1
Area (cm²)	3.8 ± 0.6
Area index (cm²/m²)	2.1 ± 0.3
Stroke volume (ml)	78 ± 17
Cardiac output (liters/min)	4.8 ± 0.9
Aortic valve	
Peak velocity (m/s)	1.28 ± 0.19
Peak velocity/LVOT peak velocity	1.28 ± 0.15
TVI (cm)	25.9 ± 4.6
Area (cm²)	3.0 ± 0.6
Area index (cm²/m²)	1.62 ± 0.2

BSA = body surface area; LVOT = left ventricular outflow tract; TVI = time velocity integral.

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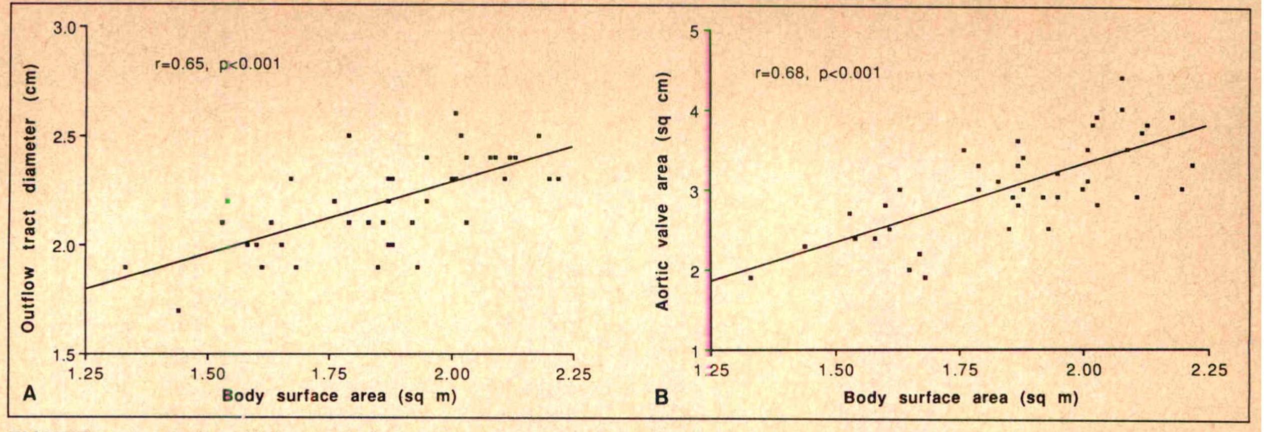

FIGURE 1. ***A*****, relation of left ventricular outflow tract diameter to body surface area in 41 normal subjects, where y = 0.99 + 0.65x, r = 0.65 and p <0.001.** ***B*****, relation of mean aortic valve area to body surface area by continuity equation in 41 normal subjects, where y = −0.56 + 1.93x, r = 0.68 and p <0.001.**

were highly reproducible, varying by no more than 0.1 cm among 3 measurements. The ratio of aortic valve area to outflow tract area was 0.80 ± 0.11. Figure 1, A and B, shows the relation of outflow tract diameter and aortic valve area to body surface area. No difference in either was seen between men and women after controlling for body surface area. Aortic valve area also increased with stroke volume (r = 0.60, p <0.01). However, stroke volume did not improve the fit between aortic valve area and body surface area, using multiple regression analysis.

In the 10 subjects studied twice, Doppler and thermodilution stroke volumes were highly concordant (r = 0.99, p <0.001) and ranged from 29 to 101 ml/beat. Aortic valve areas ranged from 1.8 to 4.3 cm^2. LV outflow tract diameter did not change between examinations. In Figure 2, the change in Doppler aortic valve area can be seen to be closely related to the change in thermodilution stroke volume. The aortic valve area changed by −12 to 11%, and stroke volume changed by −15 to 19%. Similar results were obtained when the change in LV outflow tract time-velocity integral was compared with the change in thermodilution stroke volume (r = 0.90, p <0.001). The change in aortic time velocity integral was very small and was unrelated to changing thermodilution stroke volume (r = 0.40, difference not significant).

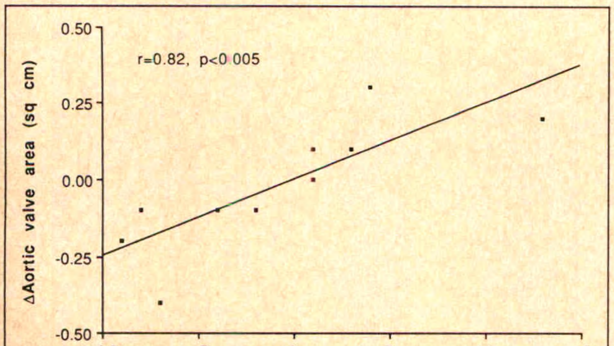

FIGURE 2. Relation of change (Δ) in mean aortic valve area to change in simultaneous thermodilution stroke volume by continuity equation in 10 subjects studied twice, where y = 0.037 + 0.035x, r = 0.82 and p <0.001.

This study establishes normal values for Doppler echocardiographic calculation of aortic valve area. The calculated aortic valve areas compare well with areas from anatomic and 2-dimensional echocardiographic studies.[4,5] LV outflow tract and aortic valve dimensions bear a close relation to body surface area. No other normal values have been reported for outflow tract dimensions, although similar data have been presented for the aortic anulus.[6,7] These values should provide a useful reference guide for learning the continuity equation method for aortic valve measurement. In hypertrophied ventricles, outflow tract dimensions are frequently smaller for any given body surface area[7]; thus, these values can be used as a guide for measurement reliability, but cannot replace direct measurement of the outflow tract. Values for outflow tract and aortic velocities are similar to those of Hatle and Angelsen.[8]

Some debate exists over whether aortic valve area varies with stroke volume in humans. Despite a small number of subjects, our findings indicate that small changes in stroke volume result in a change in mean aortic valve area, to the extent that the changes in aortic velocity are small. Differences in aortic valve area can be seen between patients with dilated cardiomyopathy and normal subjects by 2-dimensional echocardiography.[4] In dogs, opening and closing of the aortic valve requires measurable periods of time separated by a plateau of full valve opening.[9,10] Thus, maximal valve area should approximate mean aortic area in high-flow states, but may overestimate mean valve area in normal or low-flow states. M-mode studies of the aortic valve indicate that, while maximal opening is relatively insensitive to stroke volume, mean opening varies with stroke volume.[10–12] A 2-dimensional technique measuring maximal, not mean, valve area could be insensitive to smaller changes in area, such as those seen in the current study.

In subjects with small mean aortic valve areas and LV dysfunction, the question of valvar stenosis versus low flow is often raised. The continuity equation lends itself to repeated examinations of the aortic valve under varying loading conditions, which could be useful in these cases.

Even our subjects with low stroke volumes had mean aortic valve areas ≥ 1.8 cm^2 (1.1 cm^2/m^2), with an aortic valve to LV outflow tract ratio ≥ 0.57. Severe aortic stenosis usually results in mean aortic valve areas $\leq 25\%$ of the outflow tract area. Thus, clinical confusion is less likely to arise when the continuity equation technique is used to evaluate aortic stenosis in the setting of low flow.

Doppler measurement of cardiac output is often viewed as tedious and limited, because multiple measurements must be made of both flow velocity and the dimensions at the site of flow interrogation. LV outflow tract dimensions are readily and reproducibly measured because of its relative nearness and perpendicular orientation to the transducer. If its dimensions remained constant during more widely varying hemodynamic conditions, the LV outflow tract would offer an ideal spot for serial evaluation of beat-to-beat changes in stroke volume, without the need to measure outflow tract dimensions as well as flow velocity repeatedly. This hypothesis warrants further study.

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Preoperative Angiography of the Internal Mammary Artery

We read with interest the Brief Report, "Semiselective Angiography of the Internal Mammary Arteries as a Preparation for Coronary Bypass Surgery."[1] The authors state that the paper by Singh[2] was the only reported study that showed a low incidence of atherosclerosis in the internal mammary and subclavian arteries of patients with coronary artery disease. In fact, there exists a recent study[3] that also revealed a low incidence of atherosclerosis in the internal mammary arteries. As for the necessity of routine preoperative angiography of the internal mammary artery, contrary to what the authors believe, there has been no uniform sanction. To know the caliber of an internal mammary artery before operation by angiography is of theoretical value to the surgeon, because too small an artery may be unsuitable for myocardial revascularization of a large territory.[4] Additionally, in occasional patients, it would be crucial to exclude aortic or subclavian lesions proximal to the internal mammary artery, because they might significantly reduce perfusion pressure.[5,6]

Wing-Hing Chow, MB, MRCP
Tsun-Cheng Chow, MB, MRCPath
Aberdeen, Hong Kong
12 October 1990

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A Grizzly Paradox

Your editorial, "We Think We Are One. . . ," in the October 1, 1990 issue of *The American Journal of Cardiology* brought to mind a treatise I recently read on the biology of the grizzly bear,[1] a matter of more-than-passing interest to those of us who frequently travel on foot through the Canadian Rockies.

The grizzly bear and Homo sapiens have a lot in common: They are both large, intelligent, aggressive animals that are at the top of their food chain and have no natural enemies except each other. Your editorial pointed out a way in which they are evolutionarily mirror images of one another.

The grizzly bear's diet is primarily herbivorous, and it is usually only an opportunistic carnivore. (The polar bear is, I understand, alone among the bears as a pure carnivore.) The grizzly's great strength and fearsome claws evolved primarily to facilitate digging for the roots that are a major portion of its diet. The grizzly is actually a rather inefficient predator. In addition, the grizzly's gut is much more that of a carnivore than a herbivore, so that, somewhat like us, it thinks it's one thing, eats like it (more or less), but is actually the other thing. (I have no knowledge about the prevalence of ursine atherosclerosis!)

I was rather struck by the similarities between this treatise and the observations you made in your recent editorial. I greatly look forward to future thought-provoking editorials from your pen.

W.B. Firor, MD
Saskatoon, Canada
22 October 1990

1. Herrero S. Bear Attacks: Their Causes and Avoidance. New York: Nick Lyons Books, 1985.

Trifluoperazine and Spontaneous Contrast

The recent failure of trifluoperazine to resolve spontaneous contrast[1] as we reported[2] was attributed to possible changes in the gain settings of our echograph between studies or to possible changes in the apical flow patterns in the postinfarction period that may have made the detection of contrast more difficult. However, as stated in the article, repeat ultrasonic exams were performed with the same instrument settings. Furthermore, patients with left ventricular thrombus, such as our patient, are the most likely to retain the abnormal flow patterns described by Delemarre et al.[3]

Perhaps the inability to replicate our results was due to differences in methodology between their study and ours. First, only 2 mg of trifluoperazine once a day was administered by Hoffmann et al,[1] whereas our patient was receiving 2 mg twice a day when the echo contrast resolved. Second, our patient was rescanned while receiving therapy (approximately 2 to 3 hours after dosing), but those of Hoffmann et al were scanned 1 day after the last dose of trifluoperazine. The pharmacokinetic data on trifluoperazine in humans are sparse. One study reported that the half-life of trifluoperazine ranged from 7 to 18 hours with a mean of 11 hours.[4] These data are consistent with the manufacturer's recommendation that the drug be given on a b.i.d. dosing schedule.[5] The effect of trifluoperazine on platelets is dose-dependent.[6] The resolution of contrast in our patient may have been due to the higher steady-state drug concentrations, with reduced fluctuations between the minimal and maximal blood levels that would be the expected pharmacokinetic consequence of a b.i.d. dosing schedule of 2 mg, compared to a q.d. dosing of 2 mg of trifluoperazine. Another reason our patient had higher blood levels of trifluoperazine at the time of rescanning was the proximity of the repeat scan to the previous dose of trifluoperazine.

The etiology of spontaneous contrast may depend on the underlying disease process and may vary from disease to disease. Spontaneous contrast in patients with heart failure, prosthetic mitral valves, coronary artery disease in the absence of acute myocardial infarction and dilated or hypertrophic cardiomyopathies[1] may not be comparable to that in a patient with an acute infarction and a superimposed thrombus.[2] However, we would be most interested in the results of a trial of trifluoperazine using shorter dosing intervals in this patient population.

Cheryl Mahony, MD
Kevin L. Sublett, MD
Michael R. Harrison, MD
Lexington, Kentucky
31 October 1990

1. Hoffmann R, Lambertz H, Kreis A, Hanrath P. Failure of trifluoperazine to resolve spontaneous echo contrast evaluated by transesophageal echocardiography. *Am J Cardiol* 1990;66:648–650.
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3. Delemarre BJ, Visser CA, Bot H, Dunning AJ. Prediction of apical thrombus formation in acute myocardial infarction based on left ventricular spatial flow pattern. *J Am Coll Cardiol* 1990;15:355–360.
4. Gillespie TJ. Sensitive gas chromatographic determination of trifluoperazine in human plasma. *J Chromatogr* 1981;223:95–102.
5. Physicians' Desk Reference. Oradell, NJ: Medical Economics, 1990:2108–2110.
6. Kambayashi J, Morimoto K, Hakata N, Kobayashi T, Kosaki G. Involvement of calmodulin in platelet reaction. *Thromb Res* 1981;22:553–558.

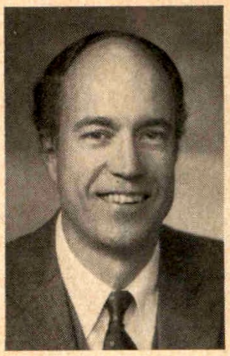
Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

Comparison of the Four Major USA Cardiology Journals in 1990: A Look at 51 Kilograms (112 Pounds) of Journals and Over 15,000 Editorial Pages

In 1984, an article appeared comparing 7 English language cardiology journals for the year 1983 in terms of numbers of editorial (non-advertising) pages, articles, types of articles, figures and tables.[1] An article comparing the 4 major USA cardiology journals also appeared in 1985.[2] A single table comparing the numbers of pages and articles and types of articles in 3 of the 4 major USA cardiology journals the previous year was published in 1988, 1989, and 1990.[3-5] This piece summarizes the results of counting the numbers of editorial pages published and the types of articles published in 1990 in the *American Heart Journal* (AHJ), *The American Journal of Cardiology* (AJC), *Circulation*, and the *Journal of the American College of Cardiology* (JACC).

Table I summarizes the numbers of pages and numbers of articles published in both the regular issues and in the symposia (or supplements) in each of the 4 journals. In the regular issues, 13,488 editorial pages *for articles* were published and in the symposia issues, 2,483 pages; 2,219 articles appeared in the regular issues and 417 articles in the symposia issues.

Table II provides data on utilization of all editorial pages—not just those for articles—in each of the 4 journals and also the types of articles published. Each journal has distinctive features. The AHJ published the most case reports (actual case descriptions), 168 or 34% of the articles published in it, whereas *Circulation* published none, JACC published only 6 and the AJC published only 23. The unique feature of the AJC is the brief reports, which are short articles with only 1 or 2 major points. They numbered 158 or 24% of the articles in the AJC, whereas only 12 were published in the AHJ and none in either *Circulation* or JACC. A major feature of *Circulation* is the large number of studies involving non-human animals (Experimental Studies). They numbered 132 or 25% of its articles, whereas 50 (9%) appeared in JACC, 29 (6%) in the AHJ and none in the AJC. The numbers of editorials were large in JACC (141 [26%]) and in *Circulation* (109 [21%]) and few in the AHJ (9 [2%]) and the AJC (33 [5%]). Reviews made up about 4% of the articles in the AHJ, *Circulation* and JACC and none appeared in the AJC. The AJC published almost as many "letters" (called Readers' Comments) as the other 3 journals combined (40 vs 46).



The symposia published in the AHJ in 1990 are listed in Table III (n = 4), those in the AJC in Table IV (n = 20), and those in *Circulation* in Table V (n = 7). None were published in JACC.

The numbers of words per page in the 4 journals are presented in Table VI. The AJC published approximately 34% more words per page than did the AHJ, 19% more than JACC, and 12% more than *Circulation.*

The numbers of subscribers of each of the 4 journals are shown in Table VII.

The regular issues of the 4 journals in 1990, including all ads and covers, weighed 43.25 kg, the symposia issues for these 4 journals weighed 5.25 kg, and the 2 abstract issues (JACC in February and *Circulation* in October) weighed 2.17 kg. The total for the regular issues, symposia issues and abstracts for 1990 was 50.67 kg (112 pounds). The 15,971 pages of articles in the regular and symposia issues averaged 1,331 pages a month, and the 2,636 articles averaged 220 a month. Happy reading.

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

1. Roberts WC. Comparison of 7 English-language cardiology journals for 1983. *Am J Cardiol* 1983;53:862–869.
2. Roberts WC. Analysis of page utilization and types of articles published in four major American cardiology journals in 1984. *Int J Cardiol* 1985;8:353–360.
3. Roberts WC. AJC Editorial Board Meeting — March 1988. *Am J Cardiol* 1988;61:1161–1164.
4. Roberts WC. Editorial board meeting of The American Journal of Cardiology — March 1989. *Am J Cardiol* 1989;63:1159–1165.
5. Roberts WC. Editorial board meeting of The American Journal of Cardiology — March 1990. *Am J Cardiol* 1990;65:1162–1168.

TABLE I Numbers of Pages for Articles and Numbers of Articles in All Issues of the Four USA Cardiology Journals in 1990

	Numbers of Pages			Numbers of Articles		
	Regular Issues	Symposia	Totals	Regular Issues	Symposia	Totals
AHJ	2,715	202	2,971	489	37	526
AJC	3,001	1,169	4,170	662	226	888
Circulation	4,346	1,112	5,458	528	154	682
JACC	3,426	0	3,426	540	0	540
Totals	13,488	2,483	15,971	2,219	417	2,636

TABLE II Numbers of Editorial (non-advertising) Pages and Articles Published in the Regular Issues (excludes symposia issues) of the Four Major USA Cardiology Journals in 1990

	American Heart Journal	American Journal of Cardiology	Circulation	Journal of the American College of Cardiology	Totals
Numbers of pages	2,911	3,498	4,967	3,753	15,129
For articles	2,715 (93.27%)	3,001 (85.79%)	4,346 (87.50%)	3,426 (91.21%)	13, 488 (89.15%)
For "letters"	17	20	33	12	82
For staff, editorial board	12	24	24	42	102
For contents in brief	59 (2.03%)	83 (2.37%)	46 (0.93%)	28 (0.75%)	216 (1.43%)
For contents with abstracts	0	233 (6.66%)	120 (2.42%)	121 (3.22%)	474 (3.13%)
For boxed abstracts	0	0	137 (2.76%)	0	137 (0.91%)
For information for authors	24	24	24	42[g]	114 (0.75%)
For meeting abstracts	0	10[b]	19[d]	0	29 (0.19%)
For erratum	0	0	4	0	4
For miscellaneous	10[a] (0.34%)	0	150[e] (3.02%)	18[h] (0.48%)	178 (1.18%)
For volume indexes	74 (2.54%)	103 (2.94%)	64 (1.29%)	64 (1.70%)	305 (2.02%)
Numbers of articles	489 (41/month)	662 (55/month)	528 (44/month)	540 (45/month)	2,219
Long reports	277	448	388	373	1,486
Concerning humans	248 (50.72%)	448 (67.67%)	256 (48.48%)	323 (59.81%)	1,275 (57.46%)
Concerning non-humans	29 (5.93%)	0	132 (25.00%)	50 (9.26%)	211 (9.51%)
Brief reports	12 (2.45%)	158 (23.87%)	0	0	170 (7.66%)
Case reports	168 (34.36%)	23 (3.47%)	0	6 (1.11%)	197 (8.88%)
Reviews	23 (4.70%)	0	31[f] (5.87%)	20 (3.70%)	74 (3.33%)
Editorials	9 (1.84%)	25 (3.78%)	109 (20.64%)	141 (26.11%)	284 (12.80%)
From the editor	0	8 (1.21%)	0	0	8 (0.36%)
Numbers of "letters" (replies)	17 (9)	40 (11)[c]	17 (12)	12 (5)	86 (37)
Annual subscription cost in USA	$65.00	$66.00	$84.00	$82.00	$297.00
Individual journals/year	12	24	12	14	62
Weight of journals/year in kg (lbs)[i]	7.65 (16.86)	10.20 (22.49)	12.26 (27.03)	13.14 (28.97)	43.25 (95.35)

[a] Includes "Bookshelf" and "Acknowledgment to Reviewers."
[b] Includes 38 abstracts of the annual meeting of the Section on Cardiology of the American Academy of Pediatrics.
[c] Letters to the Editor are called "Readers' Comments" in this journal.
[d] Includes abstracts of the 30th Annual Conference on Cardiovascular Disease Epidemiology.
[e] Includes "News from the American Heart Association," "Meetings Calendar" (domestic and abroad), and table of contents of 4 other American Heart Association journals (*Arteriosclerosis, Circulation Research, Hypertension* and *Stroke*), and "In Appreciation" to non-board reviewers.
[f] Includes American Heart Association Medical/Scientific Statements.
[g] Fourteen of the pages (The reference format one. . .) is included among the numbered editorial pages; the other 28, among the "A" (advertising) pages.
[h] Includes "newly elected members of the College, Board of Governors, Books Received, American College of Cardiology News, Committee appointments, and Participants in Bethesda Conference.
[i] Includes journal as received from the printer. Therefore, it includes the advertisements, covers, etc.

TABLE III Symposia Published in the *American Heart Journal* in 1990

1990 Date of Publication	Subject of Symposium	Guest Editor(s)	Sponsor	Number of Articles	Number of Discussions	Number of Pages	Interval (months) Symposium to Publication
February	Nicardipine	Joel A. Kaplan Michael A. Weber	DuPont Pharmaceuticals Syntex Laboratories	10	0	54	11
March	Costs and benefits of coronary risk factor reduction	C. Mancia	Pfizer International	13	4	66	8
August*	Metoprolol OROS	—	CIBA-GEIGY	5	0	28	—
September*	Nitrates for myocardial ischemia	Jonathan Abrams	CIBA-GEIGY	9	2	54	9
Totals				37	6	202	9 (mean)

* Included within the regular issues of these months.

TABLE IV Symposia Published in *The American Journal of Cardiology* in 1990

	1990 Date of Publication	Subject of Symposium	Guest Editor(s)	Sponsor	Number of Articles	Number of Discussions	Number of Pages	Interval (months) Symposium to Publication
A	January 2	Sotalol	Bramah N. Singh	Bristol-Myers	12	4	88	13
B	January 16	Cardiac arrhythmia suppression trial	Craig M. Pratt	Parke-Davis	7	0	42	5
C	February 2	Thrombosis and anti-thrombotic therapy	Valentin Fuster William C. Roberts	DuPont Pharmaceuticals	11	0	54	9
D	February 20	Moricizine HCl	Joel Morganroth J. Thomas Bigger, Jr	DuPont Pharmaceuticals	12	1	71	4
E	March 6	Hypokalemia in congestive heart failure	Milton Packer	Key Pharmaceuticals	8	2	52	—
F	March 20	Hypercholesterolemia and lovastatin	William C. Roberts Gerd Assmann	Merck Sharp & Dohme	10	0	43	9
G	April 3	Systemic hypertension	Bodo E. Strauer	Bayer AG Schwarz Pharma GmbH Merck Sharp & Dohme GmbH	16	0	88	9
H	May 2	Indapamide	Helios Pardell Paul M. Vanhoutte	Institut de Recherches Internationales Servier	16	0	80	12
I	May 22	Angiotensin-converting enzyme inhibitors	William W. Parmley	Merck Sharp & Dohme	10	0	53	14
J	June 4	Nitrate therapy	Adam Schneeweiss Marija Weiss	C.V.R.F. and Schwarz Pharma	13	0	56	—
K	June 19	Aldosteronism and aldosterone antagonism	David P. Lauler	G.D. Searle	19	0	57	—
A	September 4	High-density lipoprotein cholesterol	Antonio M. Gotto, Jr	Parke-Davis	7	1	31	12
B	September 18	Lovastatin	Scott M. Grundy	Merck Sharp & Dohme	7	0	55	10
C	September 25	Acebutolol after acute myocardial infarction	William H. Frishman Stanley H. Taylor	Rhône-Poulenc Sante	11	0	55	6
D	October 2	Angiotensin-converting enzyme inhibitors for heart failure	Jay N. Cohn	Merck Sharp & Dohme	7	0	45	8
E	October 16	Technetium-99 m myocardial perfusion imaging agents	Daniel S. Berman	DuPont Company	16	0	96	8
F	October 26	Cardiac imaging	Jeffrey A. Brinker Gerald L. Wolf	Winthrop Pharmaceuticals, Diagnostic Imaging Division	12	0	62	6
G	November 6	Factors triggering conversion from chronic to acute coronary syndromes	James E. Muller Geoffrey H. Tofler	Bristol-Myers Squibb	18	0	70	18
H	November 20	Managing ischemic myocardium	Robert A. Kloner	Pfizer Laboratories	6	0	31	12
I	December 18	Antiatherosclerotic effects of verapamil	William W. Parmley	GD Searle and Knoll Pharmaceuticals	8	0	40	9
20	Totals				226	8	1,169	10 (mean)

TABLE V Supplements* to *Circulation* Published in 1990

	1990 Date of Publication	Subject of Symposium	Guest Editor(s)	Industry Sponsor	No. of Articles	No. of Discussions	No. of Pages	Interval (mo) Symposium to Publication
I	*January*	Thromboxane A_2 antagonism in acute coronary syndromes	Attilio Maseri	Glaxo Pharmaceuticals	17	1	82	24
II	January	Measuring functional capacity in heart failure	Karlman Wasserman	Merck & Co.	7	0	64	—
III	February	Diastolic function in heart failure	Hubert Pouleur	ICI Pharmaceuticals Merck Sharp & Dohme Syntex Research	21	0	158	16
IV	March	Interventional cardiology	Kenneth M. Kent	Alpha Therapeutic Corp.	16	0	116	16
I	August	Sympathetic nervous system in heart failure	Milton Packer	ICI Pharmaceuticals	13	0	113	—
II	September	New concepts in heart failure	Richard Gorlin	ICI Pharmaceuticals Stuart Pharmaceuticals	19	0	160	20
IV	November	Cardiovascular surgery	D. Craig Miller	0	61	0	419	12
	Totals				154	1	1,112	18 (mean)

* Excludes the abstracts from the 63rd Scientific Sessions of the American Heart Association.

TABLE VI Number of Lines/Column and Words/Page in the Four Major Cardiology Journals in 1990

Journal	No. of Columns per Page	Lines per Column	Average Words per Column Line	Words per Page
AHJ	2	54	6.8	740
AJC	2	62	9.0	1,115
Circulation	2	61	8.0	980
JACC	2	53	8.5	900

TABLE VII Statement of Ownership, Management and Circulation of the Four Major USA Cardiology Journals in 1990

Journal	Filing Date	Mean No. of Copies Printed Each Month	Mean No. of Copies Distributed Each Month	Mean Paid Circulation Each Month
AHJ	10/1/90	13,200	12,500	11,800
AJC	9/20/90	32,000	30,000	22,100
Circulation	10/1/90	27,200	23,600	22,400
JACC	10/1/90	29,800	25,500	24,700

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Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 3 times a month in January, April and December, 2 times in February, March, July and August, 4 times in May, June and November, and 5 times in September and October, by Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Frank Sibley, Executive Vice-President; Robert T. Brawn, Senior Vice President/General Manager; Jerry D. Neth, Senior Vice President/Publishing Operations; J.J. Walsh, Senior Vice President/Finance; Thomas J. Dellamaria, Senior Vice President/Production and Manufacturing. Executive, Editorial and Advertising Offices: 249 West 17th Street, New York, NY 10011. Printed in Easton, PA.

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Circulation records are maintained at 44 Cook Street, Denver, CO 80206. Second class postage paid at Denver, CO, and at additional mailing office. Printed in USA Trademark™ in US Patent Office.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor in Chief, The American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814. See "Instructions to Authors," page 640.

POSTMASTER: Send address changes to: The American Journal of Cardiology, P.O. Box 173377, Denver, Colorado 80217-3377.

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suggesting that occult cardiovascular disease is not responsible for the decline in cardiac output with age in patients with essential hypertension.

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Comparison of the Effects of Guanadrel Sulfate and Propranolol on Blood Pressure, Functional Capacity, Serum Lipoproteins and Glucose in Systemic Hypertension

Linda L. Darga, Mark J. Hakim, Charles P. Lucas, and Barry A. Franklin

Fifteen physically active and moderately hypertensive subjects participated in this controlled, double-blind, crossover study, which compared the effects of guanadrel sulfate and propranolol on blood pressure, and on cardiopulmonary and metabolic variables. Data suggest that propranolol, compared with the equally effective antihypertensive guanadrel sulfate, may adversely affect cardiopulmonary function during exercise, and that guanadrel sulfate, compared with placebo, may have favorable effects on carbohydrate metabolism.

597

Comparison of Ambulatory Left Ventricular Ejection Fraction and Blood Pressure in Systemic Hypertension in Patients With and Without Increased Left Ventricular Mass

Warren M. Breisblatt, Cynthia J. Wolf, Beverly McElhinny, Rosemarie Salerni, and Vivienne E. Smith

To evaluate the effects of long-standing systemic hypertension on left ventricular function during daily activities, ambulatory radionuclide monitoring of LV ejection fraction and blood pressure were performed during exercise and other structured activities in 31 hypertensive patients. This study demonstrates that transient LV dysfunction is common and may accompany excursions of blood pressure that occur during activities when LV hypertrophy complicates hypertension.

CONGESTIVE HEART FAILURE

604

Abnormal Baroreflex Control of Heart Rate in Decompensated Congestive Heart Failure and Reversal After Compensation

José A. Marin-Neto, Antonio O. Pintya, Lourenço Gallo, Jr., and Benedito C. Maciel

Baroreflex control of heart rate was assessed in 10 patients with class IV chronic congestive heart failure before and after compensation achieved by medical treatment. A significant correlation between improvement in HR responses to atropine and head-up tilt and changes in body weight was obtained. These findings show a reversible component of impaired baroreflex control of HR in severe CHF, possibly due to its congestive effects.

VALVULAR HEART DISEASE

611

Doppler Echocardiographic Study of Porcine Bioprosthetic Heart Valves in the Aortic Valve Position in Patients Without Evidence of Cardiac Dysfunction

Sharon C. Reimold, Ajit P. Yoganathan, H-W Sung, Lawrence H. Cohn, Martin G. St. John Sutton, and Richard T. Lee

Effective orifice areas determined by Doppler echocardiograms in a group of clinically stable patients 2 and 5 years after bioprosthetic heart valve replacement were compared with those determined in vitro by a left-sided heart pulse duplicator system. Doppler studies revealed deterioration in the hemodynamic performance of bioprosthetic valves over time, suggesting that serial Doppler echocardiography may be useful for identifying subclinical bioprosthetic valvular dysfunction.

616

Clinical and Doppler Echocardiographic Follow-Up After Percutaneous Balloon Valvuloplasty for Aortic Valve Stenosis

Annette Geibel, Wolfgang Kasper, Nikolaus Reifart, Thomas Faber, and Hanjörg Just

Invasive and noninvasive before-and-after studies of 36 patients with severe aortic valve stenosis who underwent percutaneous balloon valvuloplasty revealed a significant increase in aortic orifice area and a decrease in maximal instantaneous pressure gradient. During 18 months of follow-up, Doppler echocardiography revealed an accelerated progression of restenosis in the 14 patients who died and in the 8 patients who later underwent successful aortic valve replacement, as well as a tendency for stenoses to return to preprocedural severity in patients who survived and remained free of cardiac events.

MISCELLANEOUS

622

Effect of Heart Rate on Left Ventricular Diastolic Transmitral Flow Velocity Patterns Assessed by Doppler Echocardiography in Normal Subjects

Michael R. Harrison, G. Dennis Clifton, Andrew T. Pennell, and Anthony N. DeMaria, with the technical assistance of Annette Cater

To determine the influence of heart rate on the pattern of left ventricular filling as depicted by Doppler echocardiographic transmitral flow velocities, 20 young healthy subjects were evaluated with pulsed-wave Doppler echocardiography, with the sample volume placed at the mitral anulus level in the apical 4-chamber projection. Results indicate that HR influences Doppler patterns of diastolic filling, that early filling velocity is unchanged but atrial filling velocities increase as HR increases, and that, for each increase of 10 beats/min in HR, peak atrial filling velocity can be expected to increase by 8 cm/s.

628

Effects of the Immunosuppressant Cyclosporine on the Circulation of Heart Transplant Recipients

John P. Scott, Tim W. Higenbottam, John A. Hutter, Stephen Large, and John Wallwork

Is there a direct relation between cyclosporine blood levels and the degree of systemic vascular resistance? In 34 heart transplant recipients receiving immunosuppressant treatment, cyclosporine appeared to have a direct effect as well as an unexplained chronotropic effect on systemically resistant blood vessels.

633

Effects of Exercise Training on Cardiorespiratory Function in Men and Women >60 Years of Age

James A. Blumenthal, Charles F. Emery, David J. Madden, R. Edward Coleman, Margaret W. Riddle, Susan Schniebolk, Frederick R. Cobb, Martin J. Sullivan, and Michael B. Higginbotham

After baseline measurements of aerobic capacity and blood lipids, 101 men and women >60 years old were randomized to aerobic exercise (3 times per week for 1 hour), yoga (2 times per week for 1 hour), or a 4-month waiting list nonexercise control group. Regular aerobic exercise maintained over an

extended 14-month period of time is associated with greater cardiovascular benefits among older adults than has been previously reported.

EDITORIAL

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The American Journal of Cardiology®

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CORONARY ARTERY DISEASE

The time course of functional recovery after streptokinase therapy was investigated in a controlled study of 64 patients randomized within 3 hours after the onset of acute myocardial infarction (AMI). At cardiac catheterization performed a mean of 1.5 days after AMI, streptokinase patients had less severe hypokinesia in the central and peripheral infarct regions than control patients, and a slightly higher ejection fraction. Repeat ventriculography at 5 weeks revealed further improvement in streptokinase patients only. Thus, streptokinase improves left ventricular function during the period of myocardial stunning.

The antiischemic properties of nisoldipine, 10 mg twice daily, were assessed in a double-blind, placebo-controlled, multicenter trial of 82 patients by repeated exercise tests and 72-hour ambulatory electrocardiographic monitoring. In the 41 patients receiving nisoldipine, all exercise parameters (exercise duration, time to 1 mm of ST depression, time to pain and maximal ST depression) improved. Of the ambulatory electrocardiographic monitoring parameters, only the number of ischemic episodes was reduced from 14.4 to 11.6 per patient. No significant adverse effects were observed.

Data were obtained and analyzed in 229 patients with acute myocardial infarction admitted to the coronary care unit. The patients were classified

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into 2 groups: patients without or with only mild left ventricular failure (Killip class I or II) during their hospital stay (group I), and patients who were in Killip class I or II on admission but developed cardiogenic shock during hospitalization (group II). Discriminant function analysis was performed on selected clinical and laboratory variables. Variables that were found to significantly discriminate the 2 groups of patients were age, previous infarction, x-ray cardiothoracic ratio, blood urea and lactate concentration. The risk index was computed, and blood lactate was found to be a variable with the greatest predictive power for shock development. With a cutoff value of 2 for the risk index, the sensitivity, specificity, positive and negative predictive values for shock development were 53, 99, 82 and 96%, respectively.

569

Long-Term Follow-Up of the First 56 Patients Treated with Intracoronary Self-Expanding Stents (The Lausanne Experience)

Jean-Jacques Goy, Ulrich Sigwart, Pierre Vogt, Jean-Christophe Stauffer, Urs Kaufmann, Philippe Urban, and Lukas Kappenberger

Long-term follow-up of the first 56 patients treated with the self-expanding intracoronary stent for acute occlusion during percutaneous transluminal coronary angioplasty (PTCA) or restenosis revealed successful deployment in 55 patients. Thirty-four months after implantation, 49 patients are alive, 39 remain asymptomatic and 44 are in a better functional class than before implantation. Occlusion of the stent was the most frequent major complication and occurred in 8 patients. Coronary artery bypass grafting was necessary in 4 patients and restenosis was documented in 5 patients (9%). Myocardial infarction occurred in 8 patients. Seventy-nine percent of the major complications occurred in patients with a stent in the left anterior descending coronary artery. We conclude that the self-expanding stent is a new therapeutic option for the treatment of some patients with acute occlusion or restenosis after PTCA. However, occlusion remains the major limitation of this method.

573

Capabilities of Supine Exercise Electrocardiography Versus Exercise Radionuclide Angiography in Predicting Coronary Events

Robert D. Simari, Todd D. Miller, Alan R. Zinsmeister, and Raymond J. Gibbons

Separate logistic regression models previously developed using supine exercise electrocardiography and exercise radionuclide angiography variables to predict left main or 3-vessel coronary artery disease were compared for their prognostic capabilities in 265 patients with normal resting electrocardiograms who were not taking digoxin. The exercise electrocardiography model (chi-square = 30.8, $p < 0.0001$) was a powerful predictor of future cardiac events and was similar to the exercise radionuclide angiography model (chi-square = 31.8, $p < 0.0001$). There were no differences in event-free survival for patient subgroups predicted to have low, intermediate or high probability of severe coronary artery disease using the exercise electrocardiography versus the exercise radionuclide angiography model.

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (The CASCADE Study)

The CASCADE Investigators

This randomized study evaluates survivors of out-of-hospital ventricular fibrillation (VF) not associated with a Q-wave myocardial infarction who are deemed to be at a high risk of recurrence of VF. It compares the outcome of treatment with empirically administered amiodarone with the outcome of treatment with other antiarrhythmic agents guided by electrophysiologic testing or Holter recording, or both. The primary end point of the study is total cardiac mortality. By May 1990, 199 patients had been enrolled. Of the first 142 patients, 17% had either VF or presumed arrhythmic death at 1 year. Because of this relatively high mortality, the investigators concluded that all patients participating in the study should also have an automatic defibrillator implanted when possible. Enrollment will continue until March 31, 1991.

SYSTEMIC HYPERTENSION

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Relation of Cardiac Output at Rest and During Exercise to Age in Essential Hypertension

Robert Fagard and Jan Staessen

The relation of cardiac output to age was analyzed in 110 sixteen- to 64-year-old patients with World Health Organization stage I and II essential hypertension at the time of the hemodynamic study, who were alive and free of cardiovascular complications 7 years later. At supine and seated rest, and during bicycle exercise at 50 W and at peak work load, cardiac output was inversely ($p < 0.01$) related to age. These relations were independent of weight and mean intraarterial pressure. These findings suggest that occult cardiovascular disease does not explain the decline in cardiac output with aging in patients with essential hypertension.

590

Comparison of the Effects of Guanadrel Sulfate and Propranolol on Blood Pressure, Functional Capacity, Serum Lipoproteins and Glucose in Systemic Hypertension

Linda L. Darga, Mark J. Hakim, Charles P. Lucas, and Barry A. Franklin

A double-blind comparison of the effects of guanadrel sulfate and propranolol in 15 active hypertensive subjects revealed that guanadrel sulfate decreased systolic and diastolic blood pressure (BP) at rest (−16 and −15 mm Hg, respectively) and at maximal exercise (−33 and −13 mm Hg, respectively; $p < 0.005$), without affecting aerobic capacity (maximal oxygen consumption [$\dot{V}O_2$]), ventilatory threshold, perceived exertion or standard pulmonary function measurements. Guanadrel sulfate was also associated with decreased fasting plasma glucose and serum cholesterol levels. Propranolol reduced diastolic BP at rest and systolic BP at maximal

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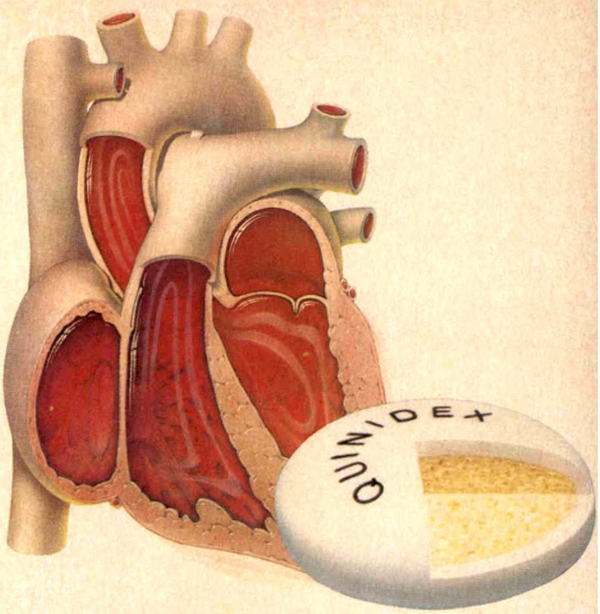

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	**Effect**
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital), phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic— Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

Twice-a-day dosing* to make life easier for your arrhythmia patients. That's the Quinidex® advantage. Because, like the heart, Quinidex Extentabs® have been uniquely constructed for dependable around-the-clock performance.

*Some patients may require t.i.d. dosing.

QUINIDEX EXTENTABS

(Quinidine Sulfate Extended release Tablets, USP) 300 mg

A·H·ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-660

exercise; however, it significantly decreased maximal $\dot{V}O_2$, ventilatory threshold, forced expiratory volume in 1 second, and increased the maximal rating of perceived exertion and serum triglyceride levels. In contrast to propranolol, guanadrel sulfate appears to decrease BP without evoking negative metabolic consequences or impairing exercise tolerance.

597

Comparison of Ambulatory Left Ventricular Ejection Fraction and Blood Pressure in Systemic Hypertension in Patients With and Without Increased Left Ventricular Mass

Warren M. Breisblatt, Cynthia J. Wolf, Beverly McElhinny, Rosemarie Salerni, and Vivienne E. Smith

To evaluate the effects of long-standing systemic hypertension on left ventricular (LV) function during daily activities, ambulatory radionuclide monitoring of LV ejection fraction and blood pressure were performed during exercise and other structured activities in 31 hypertensive patients. Patients were divided into 3 groups based on the absence of LV hypertrophy (group 1, n = 16), presence of LV hypertrophy without electrocardiographic changes (group 2, n = 10) and LV hypertrophy with associated electrocardiographic changes (group 3, n = 5). Patients in group 1 had normal ejection fraction responses to exercise and mental stress testing, as well as during routine ambulatory activities, but the responses in group 2 and 3 patients were abnormal and associated with significant increases in mean arterial pressure and reduction of diastolic filling rates. Similar abnormalities in systolic ventricular performance also occurred in group 2 and 3 patients during routine activities when blood pressure was elevated. Transient LV dysfunction is common and may occur during activities of daily living when LV hypertrophy complicates hypertension.

CONGESTIVE HEART FAILURE

604

Abnormal Baroreflex Control of Heart Rate in Decompensated Congestive Heart Failure and Reversal After Compensation

José A. Marin-Neto, Antonio O. Pintya, Lourenço Gallo, Jr., and Benedito C. Maciel

Baroreflex control of heart rate (HR) was assessed in 10 patients with class IV chronic congestive heart failure (CHF) before and after compensation achieved by medical treatment: bed rest, sodium intake restriction, diuretics and vasodilators. The mean period between the 2 studies was 15 ± 3 days. Diet and pharmacologic conditions were similar during both studies. Compensation of CHF led to significant reduction of symptomatic class, body weight, and physical, radiologic and echocardiographic signs of pulmonary and systemic congestion. Significant increases in chronotropic responses to atropine, 70° head-up tilt and handgrip were observed after compensation. Baroreflex sensitivity to phenylephrine and amyl nitrate–induced changes in blood pressure was also significantly augmented after compensation. A significant correlation was obtained between improvement in HR responses to tilt and atropine and changes in body weight seen with compensation. A reversible component of the impair-

Continued on page A26

EMINASE®

ANISTREPLASE 30 U

INDICATIONS AND USAGE: EMINASE® ANISTREPLASE, is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms **(see CLINICAL PHARMACOLOGY)**.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, EMINASE® is contraindicated in the following situations: ■ active internal bleeding ■ history of cerebrovascular accident ■ recent (within 2 months) intracranial or intraspinal surgery or trauma **(see WARNINGS)** ■ intracranial neoplasm, arteriovenous malformation, or aneurysm ■ known bleeding diathesis ■ severe, uncontrolled hypertension. EMINASE® should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

WARNINGS: Bleeding: (See ADVERSE REACTIONS) The most common complication associated with EMINASE® therapy is bleeding. The types of bleeding associated with thrombolytic therapy can be divided into two broad categories: 1. Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal, ocular, or intracranial sites. 2. Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of EMINASE® had dissipated, but while heparin therapy was continuing. As fibrin is lysed during EMINASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with EMINASE®. Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary following administration of EMINASE®, it is preferable to use an upper-extremity vessel that is accessible to manual compression. A pressure dressing should be applied, and the puncture site should be checked frequently for evidence of bleeding. Each patient being considered for therapy with EMINASE® should be carefully evaluated and anticipated benefits should be weighed against potential risks associated with therapy. In the following conditions, the risks of EMINASE® therapy may be increased and should be weighed against the anticipated benefits: ■ recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels) ■ cerebrovascular disease ■ recent gastrointestinal or genitourinary bleeding (within 10 days) ■ recent trauma (within 10 days) including cardiopulmonary resuscitation ■ hypertension: systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg ■ high likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation) ■ subacute bacterial endocarditis ■ acute pericarditis ■ hemostatic defects including those secondary to severe hepatic or renal disease ■ pregnancy ■ age >75 years (Use of EMINASE® in patients over 75 years old has not been adequately studied.) ■ diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ septic thrombophlebitis or occluded AV cannula at seriously infected site ■ patients currently receiving oral anticoagulants (e.g., warfarin sodium) ■ any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when injections of EMINASE® are administered.

Hypotension: Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis, has occasionally been observed soon after intravenous EMINASE® administration. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate symptomatic treatment should be administered.

PRECAUTIONS: General: Standard management of myocardial infarction should be implemented concomitantly with EMINASE® treatment. Invasive procedures should be minimized **(see WARNINGS)**. Anaphylactoid reactions have rarely been reported in patients who received EMINASE®. Accordingly, adequate treatment provisions such as epinephrine should be available for immediate use.

Readministration: Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE® may not be as effective if administered more than 5 days after prior EMINASE® or Streptokinase therapy or streptococcal infection, particularly between 5 days and 6 months. Increased antistreptokinase antibody levels between 5 days and 6 months after EMINASE® or Streptokinase administration may also increase the risk of allergic reactions. Repeated administration of EMINASE® within one week of the initial dose has occurred in a small number of patients treated for AMI and non-AMI conditions. The incidence of hematomas/bruising was somewhat greater in those patients who received repeat doses of EMINASE® but otherwise the adverse event profile was similar to those who received one dose.

Laboratory Tests: Intravenous administration of EMINASE® will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). Results of coagulation tests and/or measures of fibrinolytic activity performed during EMINASE® therapy may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. EMINASE®, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (2000 to 3000 KIU/mL) can, to some extent, mitigate this phenomenon.

Drug Interactions: The interaction of EMINASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin and dipyridamole) may increase the risk of bleeding if administered prior to EMINASE® therapy.

Use of Anticoagulants: EMINASE® alone or in combination with antiplatelet agents and anticoagulants may cause bleeding complications. Therefore, careful monitoring is advised, especially at arterial puncture sites. In clinical studies, a majority of patients treated received anticoagulant therapy postdosing with EMINASE® during their hospital stay and a minority received heparin pretreatment with EMINASE®. The use of antiplatelet agents increased the incidence of bleeding events similarly in patients treated with EMINASE® or nonthrombolytic therapy. There was no evidence of a synergistic effect of combined EMINASE® and antiplatelet agents on bleeding events. In addition, there was no difference in the incidence of hemorrhagic CVA's in EMINASE® treated patients who did or did not receive aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Studies to determine mutagenicity and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested.

Pregnancy (Category C): Animal reproduction studies have not been conducted with EMINASE®. It is also not known whether EMINASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EMINASE® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether EMINASE® is excreted in human milk. Because many drugs are excreted in human milk, the physician should decide whether the patient should discontinue nursing or not receive EMINASE®

Pediatric Use: Safety and effectiveness of EMINASE® in children have not been established.

ADVERSE REACTIONS: Bleeding: The incidence of bleeding (major or minor) varied widely from study to study and may depend on the use of arterial catheterization and other invasive procedures, patient population, and/or concomitant therapy. The overall incidence of bleeding in patients treated with EMINASE® in clinical trials (n=5275) was 14.6%, with nonpuncture-site bleeding occurring in 10.2%, and puncture-site bleeding occurring in 5.7%, of these patients. Bleeding at the puncture site occurred more frequently in clinical trials in which the patients underwent immediate coronary catheterization (13.3%, n=637) compared with those who did not (3.0%, n=2023). The incidence of presumed intracranial bleeding within 7 days postdosing with EMINASE® was 0.57% (n=5275; 0.34% etiology confirmed hemorrhagic; 0.23% etiology not confirmed) compared to 0.16% (n=1249) after nonthrombolytic therapy. In the AIMS trial the overall incidence of bleeding in patients treated with EMINASE® was 14.8% compared with 3.8% for placebo. The incidence of specific bleeding events was:

Type of Bleeding	EMINASE® (n=500)	Placebo (n=501)
Puncture site	4.6%	<1%
Nonpuncture site hematoma	2.8%	<1%
Hematuria/Genitourinary	2.4%	<1%
Hemoptysis	2.2%	<1%
Gastrointestinal hemorrhage	2.0%	1.4%
Intracranial	1.0%	<1%
Gum/Mouth Hemorrhage	1.0%	0
Epistaxis	<1%	<1%
Anemia	<1%	<1%
Eye Hemorrhage	<1%	<1%
Hemorrhage (unspecified)	<1%	0

In this study there was no difference between EMINASE® and placebo in the incidence of major bleeding events. Should serious bleeding (not controlled by local pressure) occur in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), any concomitant heparin should be terminated immediately and the administration of protamine to reverse heparinization should be considered. If necessary, the bleeding tendency can be reversed with appropriate replacement therapy. Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding **(see WARNINGS)**.

Cardiovascular: The most frequently reported adverse experiences in EMINASE® clinical trials (n=5275) were arrhythmia/conduction disorders which were reported in 38% of patients treated with EMINASE® and 46% of nonthrombolytic control patients. Hypotension occurred in 10.4% of patients treated with EMINASE® compared to 7.9% for patients who received nonthrombolytic treatment **(see WARNINGS)**.

Allergic-type Reactions: Anaphylactic and anaphylactoid reactions have been observed rarely (0.2%) in patients treated with EMINASE® and are similar in incidence to Streptokinase (0.1% anaphylactic shock in one study). These included symptoms such as bronchospasm or angioedema. Other milder or delayed effects such as urticaria, itching, flushing, rashes, and eosinophilia have been occasionally observed. A delayed purpuric rash appearing one to two weeks after treatment has been reported in 0.3% of patients. The rash may also be associated with arthralgia, ankle edema, gastrointestinal symptoms, mild hematuria, and mild proteinuria. This syndrome was self-limiting and without long-term sequelae.

Risk of Viral Transmission: Six batches of EMINASE® (five different batches of Lys-Plasminogen) were used in clinical trials designed specifically to monitor possible hepatitis non-A, non-B transmission. No case of hepatitis was diagnosed in patients receiving EMINASE®. Lys-Plasminogen is derived from human plasma obtained from FDA approved sources and tested for absence of viral contamination, including human immunodeficiency virus type-1 (HIV-1) and hepatitis B surface antigen. The manufacturing process includes a vapor-heat treatment step for inactivation of viruses. The entire manufacturing process has also been validated to yield a cumulative reduction of $\geq 10^{21}$ fold HIV-1 infectious particles, i.e., $\geq 10^{6}$ infectious particles removed by vapor-heat treatment and a cumulative total of $\geq 10^{15}$ infectious particles removed by the various steps in the purification process.

Causal Relationship Unknown: Since the following experiences may also be associated with AMI or other therapy, the causal relationship to EMINASE® administration is unknown. The following adverse experiences were infrequently (<10%) reported in clinical trials: **Body as a Whole**—chills, fever, headache, shock; **Cardiovascular**—cardiac rupture, chest pain, emboli; **Dermatology**—purpura, sweating; **Gastrointestinal**—nausea and/or vomiting; **Hemic and Lymphatic**—thrombocytopenia; **Metabolic and Nutritional**—elevated transaminase levels; **Musculoskeletal**—arthralgia; **Nervous**—agitation, dizziness, paresthesia, tremor, vertigo; **Respiratory**—dyspnea, lung edema.

DOSAGE AND ADMINISTRATION: Administer EMINASE® as soon as possible after the onset of symptoms. The recommended dose is 30 units of EMINASE® administered only by intravenous injection over 2 to 5 minutes into an intravenous line or vein.

Reconstitution: 1. Slowly add 5 mL of Sterile Water for Injection, U.S.P., by directing the stream of fluid against the side of the vial. 2. Gently roll the vial, mixing the dry powder and fluid. **Do not shake.** Try to minimize foaming. 3. The reconstituted preparation is a colorless to pale yellow transparent solution. Before administration, the product should be visually inspected for particulate matter and discoloration. 4. Withdraw the entire contents of the vial. 5. The reconstituted solution should not be further diluted before administration or added to any infusion fluids. No other medications should be added to the vial or syringe containing EMINASE®. 6. If EMINASE® is not administered within 30 minutes of reconstitution, it should be discarded.

HOW SUPPLIED: EMINASE® is supplied as a sterile, lyophilized powder in 30-unit vials. NDC 57294-030-20.

Storage: Store lyophilized EMINASE® between 2-8°C (36-46°F). Do not use beyond the expiration date printed on the vial.

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ment in baroreflex control of HR is suggested in severe CHF, possibly due to its congestive effects.

VALVULAR HEART DISEASE

611

Doppler Echocardiographic Study of Porcine Bioprosthetic Heart Valves in the Aortic Valve Position in Patients Without Evidence of Cardiac Dysfunction

Sharon C. Reimold, Ajit P. Yoganathan, H-W Sung, Lawrence H. Cohn, Martin G. St. John Sutton, and Richard T. Lee

Doppler echocardiograms were recorded in clinically stable patients at 2 and 5 years after replacement of native aortic valves with bioprosthetic valves. In vivo Doppler-derived effective orifice areas were compared with in vitro measurements for the same valve size. At both 2- and 5-year follow-up examinations, the Doppler-derived area was significantly less than the in vitro area ($p < 0.0001$). The mean decrease in area between the 2 examinations was 0.25 ± 0.29 cm^2 ($p < 0.005$). Serial Doppler echocardiograms demonstrate a deterioration in the hemodynamic performance of bioprosthetic valves over time in patients with no symptoms or signs of valvular dysfunction.

616

Clinical and Doppler Echocardiographic Follow-Up After Percutaneous Balloon Valvuloplasty for Aortic Valve Stenosis

Annette Geibel, Wolfgang Kasper, Nikolaus Reifart, Thomas Faber, and Hanjörg Just

Percutaneous balloon valvuloplasty is controversially considered an alternative therapy to the surgical approach. This study of 36 patients with severe aortic valve stenosis, in which all patients were invasively and noninvasively (Doppler echocardiography) studied before and after balloon valvuloplasty, revealed a significant increase in the aortic orifice area ($p < 0.001$) and a decrease in the pressure gradient ($p < 0.001$). Patients were followed for 18 months by means of clinical parameters (mortality, morbidity, clinical symptoms) and repeat Doppler echocardiographic measurements. In-hospital mortality was 8%. After hospital discharge, 16 patients (44%) died and 8 patients (22%) underwent successful aortic valve replacement. Nine patients (25%) were event-free and alive after 18 months of follow-up. Progression of restenosis assessed by Doppler echocardiography was accelerated in patients who subsequently died or underwent repeat balloon valvuloplasty or aortic valve replacement. Over a period of <6 months, aortic valve orifice area and the maximal instantaneous gradient nearly returned to preprocedural values in almost all patients.

Continued on page A30

MISCELLANEOUS

622

Effect of Heart Rate on Left Ventricular Diastolic Transmitral Flow Velocity Patterns Assessed by Doppler Echocardiography in Normal Subjects

Michael R. Harrison, G. Dennis Clifton, Andrew T. Pennell, and Anthony N. DeMaria, with the technical assistance of Annette Cater

Twenty volunteers were evaluated with pulsed-wave Doppler echocardiography, performed with the sample volume placed at the mitral anulus level. Measurements were recorded during baseline (sinus rhythm, mean 70 beats/min) and during transesophageal atrial pacing (mean 88 beats/min). Baseline peak and integrated atrial velocities averaged 0.37 ± 0.06 m/s and 2.3 ± 0.7 cm, respectively, but were significantly greater at the higher rate (0.5 ± 0.07 m/s and 3.2 ± 1.1 cm, respectively [$p < 0.003$ vs baseline for each]). Further analysis of a subgroup of 9 subjects for whom Doppler measurements were available at 3 heart rates (HRs) (sinus 70; pacing 80 and 90) yielded strong evidence for a linear relation between HR and peak atrial velocity ($A = 0.008\ HR - 0.21$, with $p < 0.0001$ for significance of the linear trend). It is concluded that HR influences Doppler patterns of diastolic filling in humans, that early filling velocity is unchanged but atrial filling velocities increase as HR is elevated, and that for each increase of 10 beats/min in HR, peak atrial filling velocity can be expected to increase by 8 cm/s.

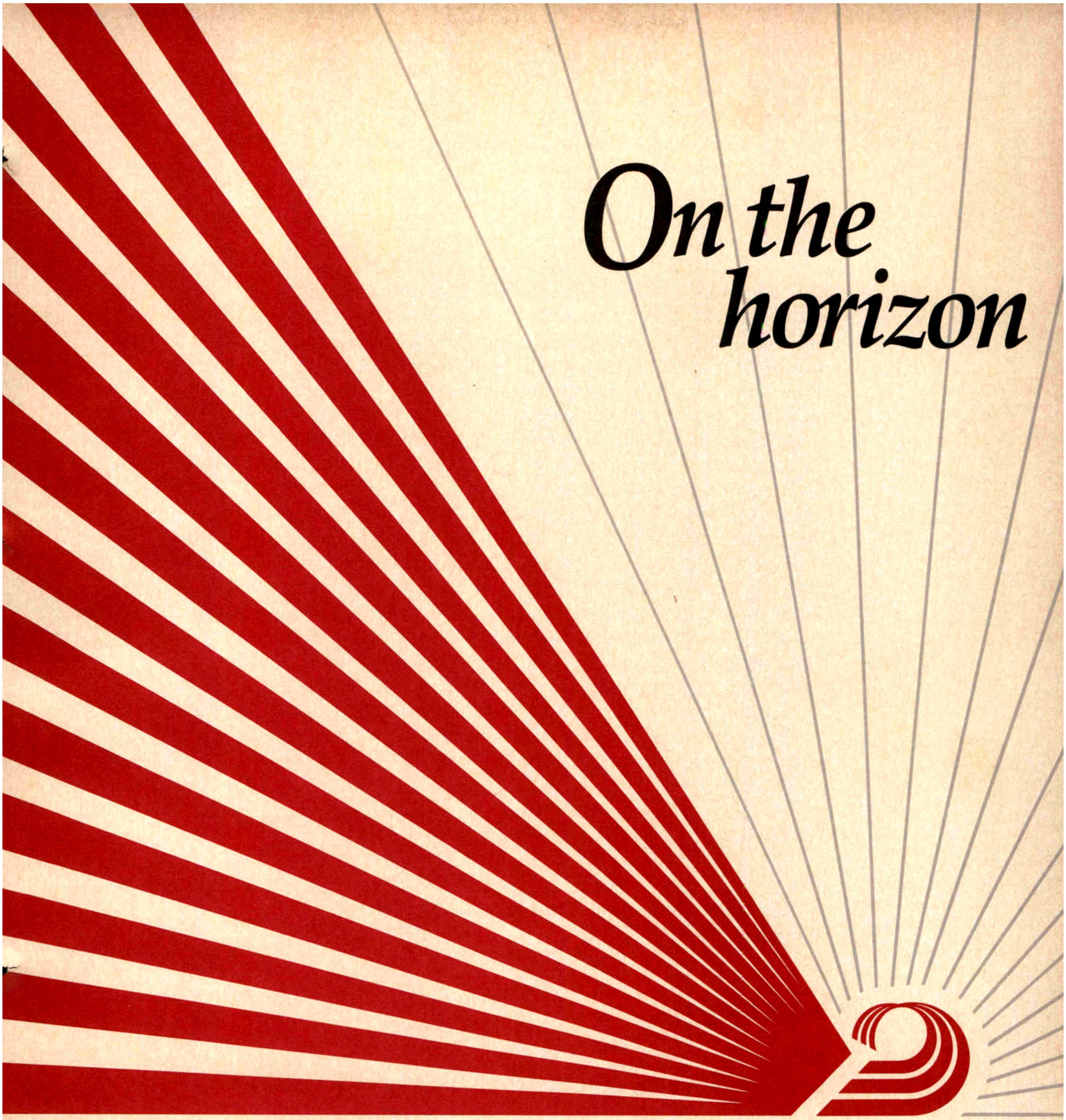
628

Effects of the Immunosuppressant Cyclosporine on the Circulation of Heart Transplant Recipients

John P. Scott, Tim W. Higenbottam, John A. Hutter, Stephen Large, and John Wallwork

To determine whether immunosuppressant treatment with cyclosporine influences vascular resistance as well as heart rate, we measured pulmonary and systemic vascular resistance at rest and after vasodilatation in 34 heart transplant recipients. A direct linear relation was found between systemic and pulmonary vascular resistance and cyclosporine trough blood levels, which were negatively related to heart rate. Cyclosporine trough blood levels may have a direct effect on systemic vascular resistance as well as an unexplained chronotropic effect on heart rate.

Continued on page A32



On the horizon

DynaCirc®
(isradipine)

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

Allen & Hanburys™
DIVISION OF GLAXO INC.

This study reports the physiologic effects of up to 14 months of aerobic exercise in 101 older (>60 years) men and women. After an extensive baseline physiologic assessment (Time 1), in which aerobic capacity and blood lipids were measured, subjects were randomized to an aerobic exercise condition (cycle ergometry 3 times per week for 1 hour), nonaerobic yoga (2 times per week for 1 hour), or a waiting list nonexercise control group for 4 months, and then underwent a second assessment (Time 2). At the completion of the second assessment, all subjects completed 4 months of aerobic exercise and were reevaluated (Time 3). Subjects were given the option of participating in 6 additional months of supervised aerobic exercise, and all subjects completed a fourth assessment (Time 4) 14 months after their initial baseline evaluation. Results indicated that subjects generally exhibited a 10 to 15% improvement in peak oxygen consumption after 4 months of aerobic exercise training, but only 1 to 6% improvement in aerobic power with additional aerobic exercise training. On the other hand, subjects, especially men, continued to show improvements in submaximal exercise performance (i.e., anaerobic threshold), and increased high-density lipoprotein cholesterol. Maintenance of regular aerobic exercise for an extended time interval is associated with greater cardiovascular benefits among older adults than has been reported previously.

EDITORIAL

BRIEF REPORTS

Continued on page A36

LANOXIN® (DIGOXIN) TABLETS

125 μg (0.125 mg) Scored I.D. Imprint Y3B (yellow)
250 μg (0.25 mg) Scored I.D. Imprint X3A (white)
500 μg (0.5 mg) Scored I.D. Imprint T9A (green)

Before using Lanoxin Tablets, the physician should be thoroughly familiar with the basic pharmacology of this drug as well as its drug interactions, indications, and usage.

DESCRIPTION: Lanoxin is digoxin, one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium.

INDICATIONS AND USAGE:
Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:
General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section). Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section). Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section in the complete prescribing information.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil*, and *amiodarone* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since this may impair the excretion of digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section and Serum Digoxin Concentrations subsection of DOSAGE AND ADMINISTRATION). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:
Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g. PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy and psychosis can occur.

Other—Gynecomastia is occasionally observed. Maculopapular rash or other skin reactions are rarely observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

OVERDOSAGE:
Treatment of Arrhythmias Produced by Overdosage:
Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Correction of factors that may contribute to toxicity such as electrolyte disturbances, hypoxia, acid-base disturbances and removal of aggravating agents such as catecholamines, should also be considered. Potassium salts may be indicated, particularly if hypokalemia is present. Potassium administration may be dangerous in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection below). Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 mL) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, atropine and/or temporary ventricular pacing may be beneficial. Digibind®, Digoxin Immune Fab (Ovine), can be used to reverse potentially life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within ½ hour of Digibind administration. Each 40 mg vial of Digibind will neutralize 0.6 mg of digoxin (which is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

In deciding the dose of digoxin, several factors must be considered:
1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

Consult complete product information before prescribing.

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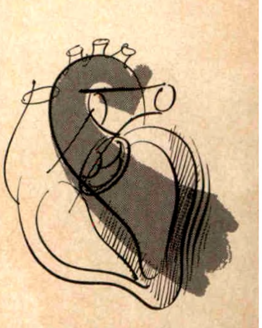

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CASE REPORTS

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The American Journal of Cardiology

MARCH 15, 1991, VOL. 67, NO. 7

Early Beneficial Effect of Streptokinase on Left Ventricular Function in Acute Myocardial Infarction

Florence H. Sheehan, MD, Claude Thery, MD, Philippe Durand, MD, Michel E. Bertrand, MD, and Edward L. Bolson, MS

The effect of intravenous streptokinase therapy on the time course of functional recovery was investigated in a controlled study of 64 patients randomized within 3 hours after the onset of acute myocardial infarction (AMI). Contrast ventriculography was performed 1 to 4 days after AMI and repeated 5 weeks later. Wall motion was analyzed by the centerline method in the central infarct, peripheral infarct and noninfarct regions. In patients with ventriculographic data at the early catheterization, streptokinase-treated patients had less severe hypokinesia in the central infarct region than control patients (−2.9 ± 0.9 [n = 29] vs −3.4 ± 0.7 standard deviations below normal [n = 21], p <0.05). The benefit of streptokinase was more marked in the peripheral infarct region (−1.5 ± 0.7 vs −2.1 ± 0.6, p <0.001). As a result, the ejection fraction was slightly higher in treated versus control groups (46 ± 10 vs 43 ± 7%, respectively; difference not significant). At 5 weeks, function in the streptokinase and control groups had diverged further because of continued improvement in the streptokinase-treated patients.

This study shows that streptokinase benefits left ventricular (LV) function by 1 to 4 days after AMI, earlier than previously reported. The benefit was not limited to the peripheral infarct region, where ischemia might have been less severe, but was also seen in the central infarct region. The implication is that thrombolytic therapy can improve LV function during the period of myocardial stunning, while myocardial function is still recovering.

(Am J Cardiol 1991;67:555–558)

From the Cardiovascular Research and Training Center, University of Washington, Seattle, Washington, and the Service de Soins Intensifs et Service de Cardiologie B et Hemodynamique, Hopital Cardiologique, Lille, France. This study was supported in part by Grant HL-19451 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and by a grant from the John L. Locke, Jr., Charitable Trust, Seattle, Washington. Manuscript received August 28, 1990; revised manuscript received and accepted November 13, 1990.

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In experimental studies, reperfusion after even brief periods of coronary artery occlusion is attended by protracted left ventricular (LV) dysfunction in the ischemic region.[1] Recovery is seen earlier in the peripheral infarct region, where ischemia is less severe, than in the central infarct region.[2,3] Clinical data on the time course of functional recovery are limited. In patients treated with thrombolytic therapy within 6 to 8 hours after symptom onset, wall motion in the infarct region begins to recover 3 to 5 days after acute myocardial infarction (AMI).[4–6]

Thrombolytic therapy has been shown to benefit LV function by the time of hospital discharge. Whether it can shorten the period of "stunning" and accelerate functional recovery is less well studied. Two studies have associated thrombolytic therapy with a significantly higher ejection fraction <1 week after AMI.[7,8] A third, the Lille streptokinase study, found no significant difference in ejection fraction between treated and control patients when measured 1 to 4 days after onset of AMI, but treated patients with anterior infarcts had better wall motion.[9] The present analysis of the Lille data was undertaken to define the nature of this early benefit to regional LV function, particularly in the peripheral infarct region, where the earliest recovery might occur.

METHODS

Patients: The study comprised 64 patients with chest pain typical of AMI who could be randomized <3 hours after symptom onset, were <75 years old, lacked a prior AMI, had ≥2 mm ST-segment elevation on the admission electrocardiogram, and had no contraindication to streptokinase therapy.[9]

Treatment protocol: Standard medical care in the cardiac care unit was comparable in the 2 groups. Those randomized to treatment received 5,000 IU of heparin intravenously, 50 mg of hydrocortisone and 0.5 g of acetylsalicylic acid, 1.5 million IU of streptokinase over 60 minutes, and then 10,000 IU of heparin. After 24 hours, the heparin dose was regulated to elevate the partial thromboplastin time to 2 to 3 times control. Those with a severe residual stenosis underwent angioplasty; coronary bypass surgery was performed for left

main coronary artery stenosis. Control patients received low-dose heparin for 3 days.

Cardiac catheterization was performed on the first weekday after admission (mean 1.5 days, range 1 to 4) and again 5 weeks after AMI. Contrast ventriculography was recorded in the 30° right anterior oblique projection. The cine films were analyzed at the University of Washington. Infarct artery patency was defined as flow grade 2 or 3 by Thrombolysis in Myocardial Infarction trial criteria.[10] Volume was calculated using the area-length method. Wall motion was measured by the centerline method[11] (Figure 1) in the central infarct, noninfarct and peripheral infarct regions,[6] without knowledge of treatment allocation, and expressed in units of standard deviations below normal, as defined in 52 normal patients.

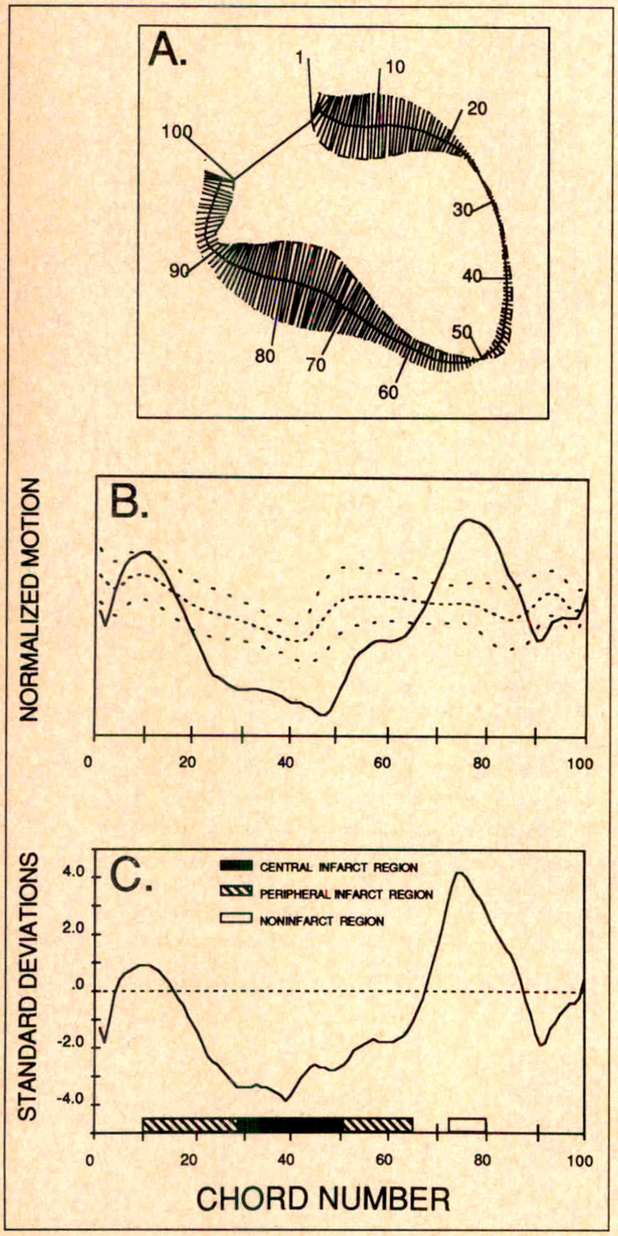

FIGURE 1. Centerline method of wall motion analysis. *A*, centerline is constructed midway between the end-diastolic and end-systolic endocardial contours. Motion is measured along 100 chords constructed perpendicular to the centerline. *B*, motion at each chord is normalized by the end-diastolic perimeter length to yield a shortening fraction. The patient's motion is plotted *(solid line)* in comparison with the mean motion ± 1 standard deviation measured in a normal population *(dashed lines)*. *C*, the patient's wall motion is plotted in units of standard deviations from the normal mean *(dashed line)*. Wall motion abnormality in the central infarct, peripheral infarct and noninfarct regions is calculated by averaging the motion of chords lying within these regions. See Methods for region description.

Statistical analysis: Treatment groups were compared using the t test for continuous variables and chi-square for proportions. Change in function between the 2 studies was assessed with the paired t test.

RESULTS

Patients: Early cardiac catheterization was performed in 33 streptokinase-treated (2 patients died) and 24 control patients (1 died, 4 refused). LV function data were available in 29 treated and 21 control patients (1 film was unretrievable; 5 were rejected). These groups were comparable in coronary pathology (Table I). Infarct artery patency was higher in treated patients (86 vs 29%, $p < 0.001$). Ventriculographic data at 5 weeks were available in 25 treated and 15 control patients; early and late function could be compared in 22 treated and 12 control patients.

Data analysis: Ejection fraction values in Seattle were lower (54 ± 12%) than reported from Lille (48 ± 10%, $p < 0.001$) because of a difference between the 2 laboratories in measuring end-diastolic volume (108 ± 27 vs 99 ± 23 ml, respectively; $p < 0.02$) but not end-systolic volume (52 ± 22 vs 52 ± 17 ml, respectively; difference not significant). The ejection fractions correlated closely ($r = 0.81$), and differences between treatment groups were statistically similar for Lille and Seattle data. The Seattle wall motion data and ejection fractions are reported here.

Ventricular function at early study (Table II): As previously reported, the global ejection fraction was slightly higher in treated than in control patients. Streptokinase benefited wall motion more significantly in the

TABLE I Baseline Characteristics by Treatment Group in Patients with Ventriculographic Data from the Early Cardiac Catheterization

	Streptokinase	Control	p Value
Number of patients	32	24	
Age (yr)	55 ± 7	54 ± 10	NS
Male/female	29/3	23/1	NS
Time from symptom onset to treatment (hrs)	2.4 ± 0.6	—	—
Time to first catheterization (hrs)	42 ± 19	41 ± 25	NS
Infarct-related coronary artery (%)			
Left anterior descending	13 (41)	10 (42)	
Right	16 (50)	9 (37)	NS
Left circumflex	3 (9)	5 (21)	
Number of coronary arteries narrowed >50% in diameter (%)			
1	27 (84)	15 (63)	
2	4 (13)	8 (33)	NS
3	1 (3)	1 (4)	

NS = difference not significant.

peripheral than in the central infarct region (Figure 2). Similar differences between treated and control patients were seen in subgroups with an anterior or inferior AMI, but were significant only in the latter (Figure 3).

Ventricular function at five weeks after infarction: As previously reported, the ejection fraction in streptokinase-treated patients was significantly higher at 5 weeks (Table II). The benefit of treatment on wall motion was also more marked at this time than 1 to 4 days after AMI. Comparison of early and late studies in streptokinase-treated patients showed significant improvement in regional and global function. LV function did not change in control patients, except for a decline in the noninfarct region.

DISCUSSION

The present study demonstrates that streptokinase can benefit function at a time when the myocardium is believed to be stunned.[1] Indeed, serial studies in humans suggest that recovery is delayed for ≥3 days after reperfusion.[4,6] The early beneficial effect observed in the present study probably reflects the alacrity with which streptokinase was administered. In experimental studies, functional recovery is delayed longer if coronary occlusion is prolonged.[2] In all 3 clinical trials reporting an early functional benefit, the thrombolytic agent was given early. In the Dutch study, streptokinase was administered at a mean of 3.2 hours: The ejection fraction at 2 to 4 days was significantly higher than in control patients.[7] In the controlled study of Maublant et al,[8] anistreplase given at 3.1 hours resulted in a higher ejection fraction at 2 to 7 days (mean 4). In the present study, streptokinase was given even earlier, at 2.5 hours, and the benefit was seen at 1 to 4 days. Without serial studies, it is impossible to pinpoint when the treated and control patients' function diverged in any of these studies. However, the present study reports the earliest time (mean 1.5 days) that thrombolytic therapy has been found to benefit function, except for the report of Rentrop et al[12] of immediate improvement after reperfusion, which others were unable to confirm.[13]

In the present study[9] and in that of Maublant et al,[8] angioplasty was performed after the end point catheter-

TABLE II Effect of Treatment on Left Ventricular Function

	Streptokinase	Control	p Value
Study 1 (1 to 4 days)			
Central infarct region (SD/chord)	−2.9 ± 0.9	−3.4 ± 0.7	0.028
Peripheral infarct region (SD/chord)	−1.5 ± 0.7	−2.1 ± 0.6	0.001
Noninfarct region (SD/chord)	−0.2 ± 0.8	−0.3 ± 0.8	NS
Global ejection fraction (%)	46 ± 10	43 ± 7	NS
Number of patients	29	21	
Study 2 (5 weeks)			
Central infarct region (SD/chord)	−2.5 ± 1.0	−3.4 ± 0.7	0.004
Peripheral infarct region (SD/chord)	−1.2 ± 0.9	−2.4 ± 0.8	<0.001
Noninfarct region (SD/chord)	−0.5 ± 1.0	−0.7 ± 0.6	NS
Global ejection fraction (%)	49 ± 10	40 ± 11	0.018
Number of patients	25	15	

NS = difference not significant; SD = standard deviations from the normal mean.

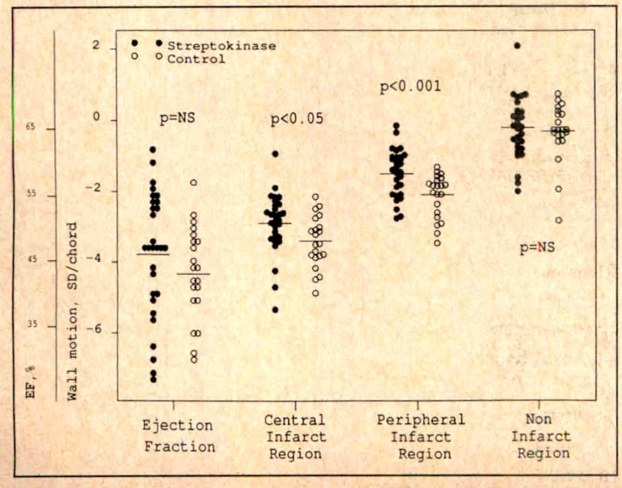

FIGURE 2. Comparison of regional and global left ventricular function 1 to 4 days after acute myocardial infarction in streptokinase-treated or control patients. EF = ejection fraction; NS = not significant; SD = standard deviation.

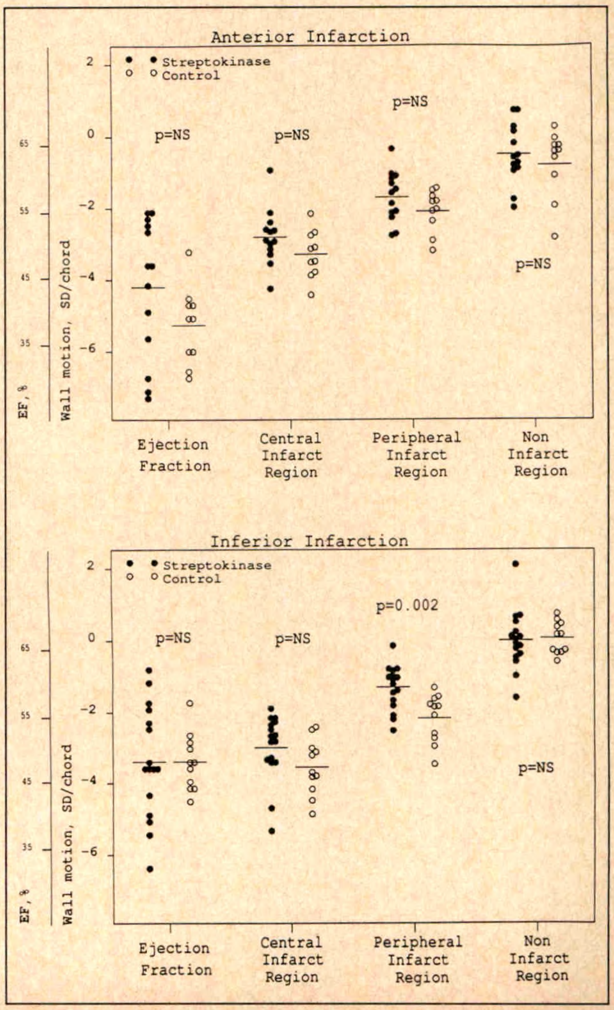

FIGURE 3. Left ventricular function at 1 to 4 days after acute myocardial infarction in streptokinase-treated and control patients, subgrouped by location of infarct either anteriorly *(top)* or inferiorly *(bottom)*. Abbreviations as in Figure 2.

ization. In the Dutch study,[7] angioplasty was performed before measuring LV function in only 11% of the patients. Therefore, it is unlikely that angioplasty contributed to the early functional benefit observed in these studies.

The hypothesis underlying thrombolytic therapy is that reperfusion salvages myocardial function and thereby enhances survival. This has been questioned recently, in light of data showing that: (1) plasminogen activator therapy benefited survival but not function,[14] and (2) treatment with streptokinase increased survival even when administered too late to salvage function.[15] Some investigators have suggested that thrombolysis may benefit survival by moderating LV dilatation and remodeling.[16]

The results of the present analysis suggest yet another avenue of benefit: salvage of LV function during the first 1 to 4 days after AMI, when mortality is highest.[17] Survival curves from clinical trials show that thrombolytic therapy exerts its greatest effect early after infarction.[7,14,18] This observation is difficult to reconcile with the belief that functional recovery is delayed. However, the present results indicate that this delay can be shortened, and stunning partially reversed, by expeditious administration of streptokinase, particularly in the peripheral infarct region. Although larger studies are needed to confirm the relation between early improvement in LV function and survival, this mechanism is supported by the Aachen streptokinase study,[6] which showed that the beneficial effect of reperfusion on LV function achieved by 3 days after AMI correlated highly with subsequent survival.

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APPENDIX

Improved Version of the Centerline Wall Motion Program

Since the description published in 1986,[11] a number of improvements have been implemented.

1. The traced borders are smoothed over 30 (not 20) points on each side of the given point.

2. After each perpendicular to the smoothed end-diastolic contour is constructed, its intersection with the end-systolic contour is sought. This search is limited to no more than $1/8$ of the border (formerly $1/6$), beginning with the last intersection found.

3. Three iterations (not 2) are made in constructing the centerline. The second proceeds counterclockwise.

4. In the previous program, no perpendicular was allowed to "cross over" the previous perpendicular. In the improved version, crossovers are allowed on the iterations in constructing the centerline, and forbidden only from the final centerline.

5. All calculations are performed in floating point (not integer). This improves accuracy primarily for frame-by-frame analysis of wall motion.

6. An error-checking mechanism is built into the program. After the 100 chords are derived from the final centerline, the distance between each adjacent pair is calculated. If 2 chords are further apart than $1/10$ of the contour, or if the number of missed intersections is excessive, then the program will vary (a) the number of points smoothed in the first step, (b) the number of iterations used to construct the centerline, or (c) the minimal distance between adjacent chords, as needed to correct the centerline, or both (b) and (c), or crossovers may be forbidden from all centerline calculations.

Effects of Nisoldipine on Myocardial Ischemia During Exercise and During Daily Activity

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The antiischemic properties of nisoldipine, a dihydropyridine calcium antagonist, were assessed in a multicenter, double-blind, placebo-controlled trial by repeated exercise testing and 72-hour ambulatory electrocardiographic monitoring in 82 patients with coronary artery disease. Patients with positive treadmill stress test results and ≥2 ischemic episodes per 24 hours were included in this study. Administration of all chronic antiischemic medications except β blockers were discontinued. During the first week all patients received placebo twice daily. During the second and third weeks, 41 patients received nisoldipine 10 mg and 41 patients received placebo twice daily. In the placebo group there were no changes in exercise parameters or in ambulatory electrocardiographic parameters. In the nisoldipine group, exercise duration increased from 403 to 448 seconds (p = 0.0035), time to 1 mm of ST depression increased from 224 to 298 seconds (p = 0.002), time to pain increased from 241 to 321 seconds (p = 0.01), and maximal ST depression was reduced from 2.6 to 2.3 mm (p = 0.002). Among the ambulatory electrocardiographic parameters in the nisoldipine group, only the number of episodes was reduced, from 14.4 to 11.6 (p = 0.0013) per patient. There was no significant reduction in total ischemic time (132 vs 120 minutes per patient). No significant side effects were observed.

This is the largest clinical trial to date on the effects of nisoldipine on myocardial ischemia. The results indicate that nisoldipine was effective in improving all exercise parameters and only partially effective in suppressing ischemia during daily activity.

(Am J Cardiol 1991;67:559–564)

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Nisoldipine is a dihydropyridine calcium entry blocking drug with a chemical structure similar to nifedipine.[1,2] Nisoldipine is well absorbed and after a single oral dose maximal plasma concentration is reached within 1.5 hours.[3] It has a slower onset of action and a longer duration than nifedipine.[4] Like all other dihydropyridine calcium antagonists its major effects consist of peripheral and coronary vasodilatation that produce improvement in myocardial oxygen supply relative to demand.[5,6] These effects occur without clinical depression of myocardial contractility or delay in electrical conduction. Nisoldipine is a potent antihypertensive agent[7,8] that can be used once or twice daily. In a limited number of clinical trials, nisoldipine has been shown to be effective and relatively well tolerated in patients with stable angina pectoris[9–12] or with congestive heart failure.[13]

This study assesses the antiischemic effects of nisoldipine in a relatively large number of stable patients with proven coronary artery disease, using repeated exercise testing and ambulatory electrocardiographic monitoring in a double-blind, placebo-controlled manner.

METHODS

Population and study protocol: Patients with known coronary artery disease and positive treadmill stress test results were considered candidates for this study in 4 medical centers in Israel.

The diagnosis of coronary artery disease was based on ≥1 of the following criteria: a documented previous myocardial infarction, angiographic evidence of significant coronary artery stenosis (>70% diameter narrowing in at least 1 major coronary artery), or typical history of effort-induced angina, or any combination of these. Prior therapy with oral nitrates, calcium entry blockers, digitalis and angiotensin-converting enzyme inhibitors were discontinued. Therapy with sublingual nitrates was allowed, and β-blocking agents in a constant dose were continued at the discretion of the patient's personal physician. To enter the study, patients had to have a positive treadmill stress test result (≥1.5 mm horizontal ST depression) and ≥2 silent ischemic episodes on ambulatory 24-hour Holter monitoring during the screening phase. Patients were excluded from the study if they had unstable angina, recent myocardial infarction (<3 months), clinical signs of congestive heart failure, or had balloon angioplasty or coronary bypass surgery within 3 months. Patients with the follow-

TABLE I Baseline Characteristics of 41 Patients in the Placebo and Nisoldipine Groups

Characteristic	Placebo (n = 41) (%)	Nisoldipine (n = 41) (%)	p Value*
Age	61 (9)	62 (7)	NS
Male gender	37 (90)	33 (80)	NS
Typical angina	41 (100)	38 (93)	NS
Anginal frequency†	6.4 (1)	7.1 (1)	NS
Diabetes	5 (12)	5 (12)	NS
Hypertension	4 (10)	8 (19)	NS
Prior angiography	20 (50)	16 (39)	NS
Multivessel disease	14 (70)	13 (81)	NS
Prior infarct	17 (41)	16 (39)	NS
Prior angioplasty	2 (5)	2 (5)	NS
Prior bypass surgery	5 (12)	2 (5)	NS
Beta blocker use	18 (44)	21 (51)	NS

* Paired *t* test.
† Episodes per week.
All values in brackets are percentages except for age, which is mean ± standard deviation. Frequency of angina is mean ± standard error of the mean.
NS = not significant.

ing characteristics were also excluded: uncontrolled severe hypertension, systolic blood pressure <90 mm Hg, significant valvular or myocardial disease, left bundle branch block, and significant ST-T abnormalities on the resting electrocardiogram; those unable to perform repeated exercise tests or those who were inactive were also excluded.

After the screening phase the patients were randomized in blinded manner to 2 treatment groups (nisoldipine 10 mg twice daily or placebo twice daily). During the first week the 2 groups received placebo twice daily. At the end of this week all had a treadmill stress test and 72-hour ambulatory electrocardiographic monitoring. During the second and third weeks, 41 patients received nisoldipine 10 mg and 41 placebo twice daily. At the end of this treatment period, treadmill stress test and 72-hour ambulatory electrocardiographic monitoring were repeated.

Eight patients withdrew from the study. Thus, 82 of the 90 patients who entered the study completed it. Two patients who withdrew during the placebo run-in period had worsening of their angina. Three of the 6 patients who withdrew during the "treatment" period belonged to the placebo group: 1 sustained an acute non-Q-wave myocardial infarction, 1 had coronary bypass surgery and 1 developed leg erysipelas. Three patients in the nisoldipine group withdrew: 1 had severe symptomatic hypotension, 1 had increasing chest pain and 1 refused to continue the study. Two additional patients, 1 in the placebo and 1 in the nisoldipine group, complained of dizziness which was not severe and they completed the study. No patient developed leg edema.

Treadmill stress test: Maximal treadmill stress testing was performed according to the Bruce protocol 2 hours after the morning medication was administered. Leads II, V_3 and V_5 were continuously monitored and every minute a rhythm strip of these leads was printed. At the end of each stage (every 3 minutes), a 12-lead electrocardiogram and blood pressure were recorded. The exercise test was terminated if (1) moderate to severe chest pain developed, (2) >3 mm of ST depression was observed, (3) >20 mm Hg decrease in systolic blood pressure occurred, (4) complex ventricular arrhythmias were observed, or (5) the patient attained target heart rate.

Holter monitoring: Ambulatory electrocardiographic monitoring was performed using ACS reel-to-reel AM 2-channel recorders. The electrodes were placed in the V_3- and V_5-like position.[14] All magnetic tapes were digitized and analyzed at Bikur Cholim Hospital on the Cardiodata Prodigy System, using version 7.07 of the ST analysis software.

An ischemic episode was defined as transient depression (horizontal or downsloping) of ST segment of ≥1 mm, which lasted for at least 1 minute and after which a return to baseline was observed.

Analysis of the ST segment was performed in both channels in a semiautomatic-interactive method. The technician had to decide on 2 points: the isoelectric line at the PR interval and the J point. The system determined the ST slope by measuring the level of the ST segment 60 ms after the J point. For each episode, electrocardiographic samples were printed out in real time 2 minutes before onset of ST depression, at the onset of ischemia (1 mm of ST depression), at maximal ST depression, at maximal heart rate and on return of the ST segment to the isoelectric line. Each episode was visually verified by the technician and the physician both from the ST trend and from the real printouts. The ST changes during the whole monitoring period were plotted in the 2-channel ST-trend histograms. A heart rate trend was plotted under the ST trend, enabling accurate determination of heart rate before and during the ischemic episodes.

For each ischemic episode the following parameters were measured: the time of occurrence, the duration in minutes, the heart rate at 1 mm of ST depression, the maximal heart rate and the maximal ST depression.

Statistical analysis: Selected clinical, exercise testing and Holter monitoring variables recorded during the placebo run-in period and during the treatment period were compared within each group (placebo and nisoldipine) using the Student's paired *t* test. All comparisons were repeated using the Mann-Whitney test. Analysis of variance was used to compare the response of the placebo group to that of the nisoldipine group. In this analysis the value of each variable of interest during the treatment period served as the dependent response variable, whereas the predictor variables included the value of each variable during the placebo run-in period, the treatment assignment (placebo or nisoldipine), concomitant β-blocker therapy (during both periods) age, gender and a prior infarction. A p value <0.05 was considered statistically significant.

RESULTS

Of the 82 patients who completed the study, 70 (85%) were men, 33 (40%) had prior myocardial infarction and 39 (47%) were taking β blockers. Forty-one patients were randomly allocated to the placebo group and 41 to the nisoldipine group. The baseline characteristics of the 2 groups were similar (Table I). The effects of placebo on clinical variables are listed in Table II. There were no differences between the 2 placebo peri-

ods in resting systolic and diastolic blood pressure, and no difference in heart rate. However, anginal frequency was reduced from 5.0 to 3.3 episodes per week, and nitroglycerin consumption from 3.0 to 2.1 tablets per week.

In the nisoldipine group (Table II) there was a significant increase in resting heart rate and a decrease in systolic and diastolic blood pressure. Anginal frequency was reduced from 5.5 to 3.1 episodes per week and nitroglycerin consumption from 3.4 to 1.8 tablets per week.

Exercise test results: Table III compares the exercise test variables in the first and the second study periods in the placebo and nisoldipine groups. In the placebo group, none of the exercise variables significantly changed. In the nisoldipine group, there was a significant increase in exercise duration (from 403 to 448 seconds, 11% increase), in time to 1 mm of ST depression (from 224 to 298 seconds, 33% increase), and in time to anginal pain (from 241 to 321 seconds, 33% increase). There was also a significant reduction in the maximal degree of ST depression and a trend to an increase in the ischemic threshold, from 112 to 116 beats/min ($p = 0.07$). In 3 of the patients, the exercise test response became normal with nisoldipine therapy. In addition, the maximal heart rate achieved increased significantly and the maximal systolic and diastolic blood pressure decreased, while there was no change in pressure-rate product at maximal exercise or at 1 mm of ST depression.

The response in exercise variables was compared between the treatment and the placebo groups using the analysis of variance technique after adjustment for the placebo run-in measurement, concomitant β-blocker

TABLE II Effects of Placebo and Nisoldipine on Baseline Clinical Parameters

	Placebo (n = 41)			Nisoldipine (n = 41)			p Value for Placebo vs Nisoldipine
Variable	Run-in	Treat.	p Value	Run-in	Treat.	p Value	
Resting HR (beats/min)	70 (11)	70 (13)	0.87	68 (12)	73 (13)	0.0049	0.029
Resting systolic BP (mm Hg)	131 (21)	129 (18)	0.38	127 (17)	117 (16)	0.0008	0.031
Resting diastolic BP (mm Hg)	81 (11)	79 (10)	0.22	78 (10)	73 (10)	0.0041	0.16
Angina (frequency/week)	5 (1)	3.3 (1)	0.0025	5.5 (0.9)	3.1 (0.7)	0.0002	0.38
Nitroglycerin (consumption/week)	3 (0.8)	2.2 (0.9)	0.016	3.4 (0.8)	1.8 (0.5)	0.0061	0.35

All values are expressed as mean ± standard deviation except for frequency of angina and nitroglycerin consumption, which are expressed as mean ± standard error of the mean.
BP = blood pressure; HR = heart rate; Treat. = treatment.

TABLE III Results of Exercise Testing in the Placebo and Nisoldipine Groups

	Placebo (n = 41)			Nisoldipine (n = 41)			p Value for Placebo vs Nisoldipine
Variable	Run-in	Treat.	p Value	Run-in	Treat.	p Value	
Maximal HR (beats/min)	129 (19)	132 (19)	0.088	126 (19)	132 (19)	0.021	0.33
Maximal systolic BP	158 (26)	156 (26)	0.39	153 (28)	146 (26)	0.021	0.23
Maximal diastolic BP	87 (13)	85 (10)	0.18	85 (14)	79 (13)	0.0011	0.10
Maximal BP × HR (mm Hg/min)	20,667 (5,369)	20,840 (5,287)	0.72	19,510 (5,660)	19,438 (5,241)	0.89	0.73
Exercise duration (sec)	423 (131)	434 (120)	0.46	403 (142)	448 (146)	0.0035	0.088
Maximal ST↓ (mm)	2.7 (0.8)	2.6 (0.9)	0.28	2.6 (0.8)	2.3 (0.9)	0.0018	0.21
Time to ST↓ (sec)	254 (114)	266 (121)	0.51	244 (110)	298 (139)	0.0002	0.017
Time to pain (sec)	305 (140)	329 (140)	NS	241 (97)	321 (156)	0.01	0.02
HR at ST↓ (beats/min)	112 (15)	112 (18)	0.82	112 (16)	116 (19)	0.077	0.11
Systolic BP (mm Hg)	148 (24)	146 (21)	0.49	145 (27)	142 (23)	0.23	0.82
BP × HR at ST↓ (mm Hg/min)	16,828 (4,394)	16,740 (4,024)	0.48	16,424 (4,576)	16,668 (4,553)	0.67	0.43

All values are expressed as mean ± standard deviation.
ST↓ = ST depression; other Abbreviations as in Table II.

therapy and several baseline characteristics. This comparison detected a significant effect of nisoldipine on changes in blood pressure, on time to 1 mm of ST depression and on time to pain. The effect of nisoldipine on exercise duration showed only a trend toward improvement ($p = 0.10$), whereas the reduction in maximal ST depression did not reach statistical significance ($p = 0.17$).

Holter monitoring results: Table IV compares the 72-hour Holter parameters between the 2 study periods in the placebo and nisoldipine groups. None of the Holter variables changed significantly in the placebo group. In the nisoldipine group the average number of ischemic episodes per patient was reduced from 14.4 to 11.6 ($p = 0.0013$); however, the reduction in total ischemia duration from 132 to 120 minutes did not reach statistical significance. In addition, there was no significant change in the mean episode duration, in mean heart rate at 1 mm of ST depression or in maximal ST depression.

When the effect of therapy on silent and symptomatic episodes was assessed (Table V), there was no significant change in the placebo group. In the nisoldipine group there was significant reduction of both the number (from 2.3 to 1.2) and duration (from 26.2 to 13.3 minutes) of symptomatic episodes, with no change in the silent episodes. When the results were categorized according to the average number of ischemic episodes per patient—>8, >12 and >16 episodes—the only parameter that remained significant was the reduction in the number of ischemic episodes with nisoldipine.

In assessing whether the effect of nisoldipine on Holter parameters was more marked at peak effect of the drug, Holter ischemic parameters recorded between

TABLE IV Effect of Placebo and Nisoldipine on Holter Parameters*

	Placebo (n = 41)			Nisoldipine (n = 41)			p Value for
Variable	Run-in	Treat.	p Value	Run-in	Treat.	p Value	Placebo vs Nisoldipine
No. of episodes	14 (9)	14.1 (9)	0.87	14.4 (7)	11.6 (7)	0.0013	0.049
Total ischemic time (min)	179 (185)	171 (199)	0.61	132 (77)	120 (106)	0.43	0.82
Mean episode duration (min)	11.5 (7)	10.3 (6)	0.20	9.4 (5)	9.5 (4)	0.88	0.27
Mean HP at ST↓ (beats/min)	96 (13)	96 (12)	0.57	93 (11)	93 (11)	0.77	0.57
Maximal ST↓	3.6 (1.5)	3.6 (1.9)	0.93	3.6 (1)	3.5 (1)	0.39	0.538

* Results expressed as average per patient per 72 hours of monitoring during treatment periods.
Abbreviations as in Table III.

TABLE V Holter Monitoring Results According to Symptoms

	Placebo (n = 41)			Nisoldipine (n = 41)			p Value for
Variable	Run-In	Treat.	p Value	Run-In	Treat.	p Value	Placebo vs Nisoldipine
Numberof episodes							
Symptomatic	1.7 (3)	1.2 (31)	0.17	2.3 (3)	1.2 (2)	0.015	0.35
Silent	12.3 (8)	13 (9)	0.50	12 (7)	10.4 (7)	0.12	0.72
Ischemic time							
Symptomatic	35 (73)	27 (59)	0.50	26 (39)	13 (23)	0.028	0.30
Silent	152 (157)	147 (163)	0.70	105 (37)	106 (108)	0.94	0.76

Treat. = treatment.

TABLE VI Additive Effect of Nisoldipine on Ischemic Parameters in 21 Patients Who Continued Therapy with Beta-Blocking Drugs

	Run-in (β blockers)	Treatment (β blockers + nisolidpine)	p Value
Exercise tests variables			
Exercise duration (sec)	365 ± 156	416 ± 137	0.013
Time to 1 mm ST↓ (sec)	191 ± 113	261 ± 78	0.0012
Maximal ST↓ (mm)	2.8 ± 0.7	2.4 ± 0.6	0.014
Holter monitoring variables			
No. of episodes/patient	15.1 ± 6.7	11.1 ± 7.3	0.0062
No. of symptomatic episodes	2 ± 3	1.2 ± 2.1	0.2
No. of silent episodes	13.1 ± 7.7	9.9 ± 6.1	0.012
Total iSchemic time (min)	118 ± 68	102	0.24

Abbreviations as in Table III.

0700 to 1200 hours were compared. The number of ischemic episodes in the placebo group did not change from the placebo run-in period to the treatment period (5.5 vs 5.0, respectively), whereas it was significantly decreased in the nisoldipine group (5.2 vs 3.9, respectively, $p = 0.01$). There was no significant change in duration of ischemia.

Effect of concomitant beta-blocker therapy: Thirty-nine patients continued to take β-blocking medications throughout the study period, and 21 were randomly assigned to the nisoldipine and 18 to the placebo groups. In the group of 21 patients taking β blockers during the run-in period (Table VI), nisoldipine significantly improved all exercise parameters, whereas only the number of ischemic episodes decreased by 27% among the Holter parameters.

DISCUSSION

The antiischemic effects of nisoldipine, a dihydropyridine calcium antagonist, were assessed in this double-blind, placebo-controlled trial by exercise testing and Holter monitoring. Nisoldipine reduced systolic and diastolic blood pressure at rest an average of 10 mm Hg. This was accompanied by a moderate but significant increase in heart rate. Nisoldipine also reduced the frequency of anginal attacks, and the weekly consumption of nitroglycerin was also reduced. A similar trend toward reduction in the number of anginal attacks and nitroglycerin consumption, though less pronounced, was observed in the placebo group; however, the difference between the groups did not reach statistical significance.

Nisoldipine improved exercise test parameters. The exercise duration increased by 11%, the time to 1 mm of ST depression increased by 33%, the time to anginal pain increased by 33%, and the maximal ST depression decreased from 2.6 to 2.3 mm.

Holter monitoring parameters showed only partial response to nisoldipine. The number of ischemic episodes was significantly reduced, from 14.4 to 11.6 episodes per patient. Nisoldipine did not significantly reduce the total ischemic time per patient. When we analyzed the silent and the symptomatic episodes separately, both the number and the duration of the symptomatic episodes were reduced by nisoldipine, whereas there was no change in the silent episodes.

Our patients were allowed to continue to take β-blocking drugs, and, thus, the additive effect of nisoldipine to that of β blockers could also be evaluated. In this group, nisoldipine improved exercise test parameters more than in the total study population, and it also decreased the frequency of ischemic episodes significantly, although the duration of ischemia was not reduced.

The discrepancy between the response to nisoldipine, as assessed by exercise testing and by Holter monitoring, is not clear. The exercise test mainly measures ischemia, which is associated with an increase in oxygen demand. Nisoldipine, like all calcium antagonists, does not reduce heart rate and is therefore expected to be more efficacious in preventing spontaneous ischemic episodes probably associated with dynamic changes in coronary tone. Cohn et al,[15] who studied the effect of nifedipine, found a 23% reduction in the number of ischemic episodes, whereas in patients with frequent ischemic episodes the reduction was 45%. In our study, the opposite was observed: Nisoldipine improved parameters of ischemia during exercise more than parameters of spontaneous ischemic episodes during daily life. It is possible that the difference between the response as measured by the 2 methods is due to the large variability in the number and duration of ischemic episodes between the placebo run-in and the nisoldipine treatment periods. Another potential source of methodologic error is the difference in duration of ischemia during the run-in-period between the placebo group (179 minutes) and the nisoldipine group (132 minutes).

In the present study, 84% of the ischemic episodes were silent. The effect of nisoldipine reached statistical significance only during the symptomatic episodes. We have no explanation for this difference. Several studies have indicated that silent ischemia is associated with similar characteristics and similar hemodynamic changes as symptomatic ischemia.[16-19] According to previous studies, nitrates,[20] β blockers[21] or calcium antagonists[22] had similar effect on silent and symptomatic episodes.

In this study, all patients received the same dose of nisoldipine. Had we used individual dose titration,[23] a larger dose of nisoldipine could have been given and the antiischemic effect would have been more pronounced.

Acknowledgment: We deeply appreciate the devoted assistance of Noa Dody and Vita Linde for the Holter interpretation, and Lea Rozental, Marina Chahmiguery and Zipora Ben-Ami.

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Usefulness of Blood Lactate as a Predictor of Shock Development in Acute Myocardial Infarction

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Data were obtained and analyzed in 229 patients admitted to the coronary care unit from November 1988 through July 1989. The patients were classified into 2 groups: patients without or with only mild left ventricular failure (Killip class I or II) during their hospital stay (group I), and patients who were in Killip class I or II on admission but developed cardiogenic shock during hospitalization (group II). Discriminant function analysis was performed using the following variables: patients' age, history of previous myocardial infarction, diabetes mellitus, blood lactate, urea, creatinine, creatine kinase, aspartate aminotransferase, lactate dehydrogenase concentrations, and chest x-ray cardiothoracic ratio. Variables that were found to significantly discriminate the 2 groups of patients were age, previous infarction, x-ray cardiothoracic ratio, blood urea and lactate concentrations. The risk index was computed, and blood lactate was the variable with the greatest predictive power for shock development. The sensitivity, specificity and predictive value of the risk index, taking various cutoff points, were calculated. With a cutoff value of 1, sensitivity was 65%, specificity 91%, positive predictive value 36% and negative predictive value 97%. With a cutoff value of 2, sensitivity was 53%, specificity 99%, positive predictive value 82% and negative predictive value 96%.

(Am J Cardiol 1991;67:565–568)

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Cardiogenic shock is a leading cause of death in patients with acute myocardial infarction (AMI). First clinical signs of cardiogenic shock in AMI are manifestations of poor peripheral perfusion, but these signs need not be the earliest indicator of inadequacy of cardiac function. Sheps[1] and Kessler[2] and their co-workers demonstrated that peripheral blood lactate determination can be a useful prognostic marker for risk of recurrent cardiac arrest; an increase in blood lactate may be related to tissue hypoperfusion. In this study we tested the hypotheses that elevated peripheral blood lactate concentration preceded clinical manifestations of shock in patients with AMI and that blood lactate could be used to predict the occurrence of shock.

METHODS

This study comprised 291 consecutive patients with AMI admitted to the coronary care unit from November 1988 through July 1989. The first 229 patients formed the study group, and the next 62 patients were used for cross-validation of the results obtained through discriminant function analysis. The diagnosis of AMI was based on the presence of ≥2 of the following criteria: characteristic history of prolonged chest pain, elevation in serial cardiac enzymes—creatine kinase, aspartate aminotransferase, lactate dehydrogenase—and characteristic electrocardiographic ST-T changes with or without development of new Q waves. When there were only ST-T changes on the electrocardiogram (without new Q waves), elevation of cardiac enzymes was required for confirmation of AMI. The patients were further classified into 2 groups. Group I consisted of patients without or with only mild left ventricular failure (Killip class I and II[3]) during their hospital stay. Group II consisted of patients who were in Killip class I or II on admittance but developed cardiogenic shock during hospitalization. Patients with cardiogenic shock already present on arrival to the coronary care unit and those who developed shock during the first 24 hours were not included in the study. Patients with Killip class III left ventricular failure, patients who died from causes other than cardiogenic shock, and patients who were resuscitated from cardiac arrest also were not included. Cardiogenic shock was defined as systolic blood pressure <90 mm Hg for >30 minutes, accompanied by the clinical signs of peripheral hypoperfusion and a decrease in urinary output (urine flow <20 ml/hour).

TABLE I Comparison Between Patients With and Without Cardiogenic Shock

	Group I (n = 212)	Group II (n = 17)	p Value
Age			
<60 years	78 (37%)	0	<0.01
≥60 years	134 (63%)	17 (100%)	
Previous AMI			
No	177 (84%)	10 (59%)	<0.05
Yes	35 (16%)	7 (41%)	
Diabetes mellitus	70 (33%)	7 (41%)	NS
Thrombolytic therapy	35 (16%)	2 (12%)	NS
Killip class II	42 (20%)	6 (35%)	NS
Cardiothoracic ratio (%)			
<55	138 (65%)	6 (35%)	<0.05
≥55	74 (35%)	11 (65%)	
<60	202 (95%)	12 (71%)	<0.001
≥60	10 (5%)	5 (29%)	
Blood urea (mmol/liter)	7.81 ± 0.16	13.32 ± 2.23	<0.001
Blood creatinine (μmol/liter)	108 ± 12	171 ± 25	NS
Creatine kinase (IU/liter)	1025 ± 48	1093 ± 78	NS
Blood lactate (mmol/liter)	2.57 ± 0.05	3.21 ± 0.38*	<0.05
		4.20 ± 0.61†	<0.001

* Mean blood lactate before appearance of shock.
† Blood lactate obtained on the day that preceded shock development.
Data are expressed as number of patients or mean ± standard error of the mean.
AMI = acute myocardial infarction; NS = not significant.

The following variables were taken into account: patients' age, history of previous AMI, diabetes mellitus, blood lactate, peak blood urea, creatinine, creatine kinase, aspartate aminotransferase and lactate dehydrogenase concentrations, chest x-ray cardiothoracic ratio, and thrombolytic therapy. Blood lactate, urea, creatinine and cardiac enzymes were measured daily, and the chest x-ray was obtained on the first or second day of hospitalization. Blood samples for lactate determination were drawn from a brachial vein without use of a tourniquet, and processed by enzymatic ultraviolet method without deproteination,[4] using a commercial kit (Boehringer-Manheim GMBH, Germany).

Statistical analysis was accomplished through SPSS computer software.[5] Multivariate analysis of variance and discriminant function analysis were performed on selected variables in the study group, and the discriminant function was cross-validated on the second group of patients. Continuous data are expressed as mean ± standard error of the mean, and discrete variables as frequencies. Differences were considered significant at $p < 0.05$.

RESULTS

Of 229 patients who formed the study group, 212 remained in Killip class I or II during their hospital stay (group I), and 17 developed cardiogenic shock (group II). Comparison between the 2 groups is presented in Table I. Sixty years was the cutoff value for age that best separated the 2 groups. The incidence of previous AMI was higher in group II than in group I. Cardiomegaly defined as x-ray cardiothoracic ratio ≥55% was found more often in group II patients, but a cutoff point for cardiothoracic ratio of 60% had a higher significance in differentiating the 2 groups. Peak blood urea concentration was higher in group II than in group I. Blood lactate (mean for group I and the mean of values obtained on days before the first appearance of clinical signs of shock for group II) was also higher in group II than in group I patients, but when mean blood lactate was compared in group I patients with the value of blood lactate obtained on the day that just preceded the appearance of shock in group II patients, a significantly higher difference was seen. This blood lactate value in group II patients was also significantly higher than individual lactate values obtained on each of 4 successive days in group I patients: 4.20 ± 0.61 vs 2.86 ± 0.09, 2.64 ± 0.07, 2.42 ± 0.06 and 2.52 ± 0.1 mmol/liter, respectively ($p < 0.05$). The daily lactate levels in the 2

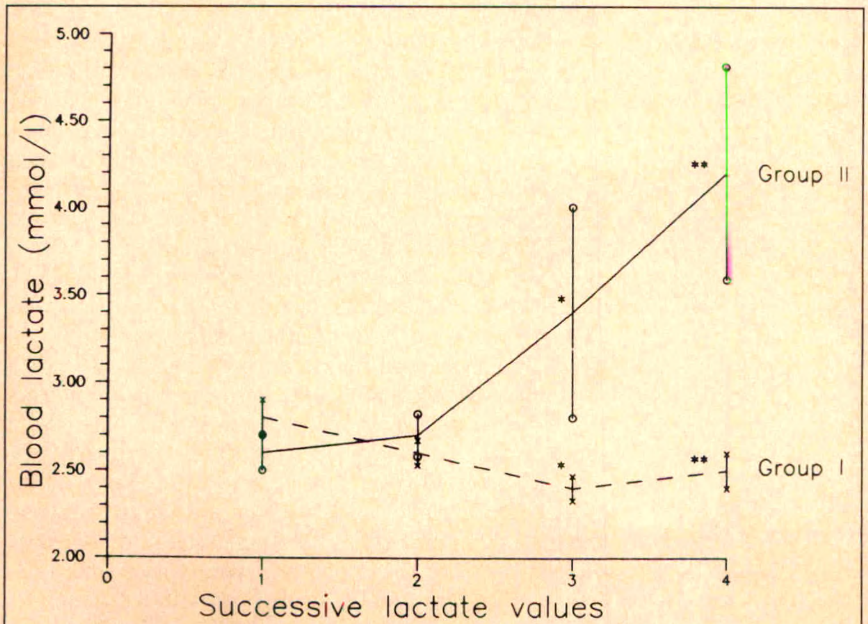

FIGURE 1. Blood lactate values obtained on successive days in 2 groups of patients. Values are expressed as mean ± standard error of the mean. Group I = patients without shock; Group II = patients who developed shock during hospi-

TABLE II Results of Discriminant Function Analysis of Selected Variables

	F1	F2	Coeff.	Corr.
Blood lactate	45*	29*	0.62	0.67
Blood urea	44*	22*	0.57	0.66
Previous AMI	6†	7†	0.31	0.26
Cardiothoracic ratio	17*	2	0.17	0.41
Age	10‡	2	0.18	0.31

* p <0.001; † p <0.05; ‡ p <0.01.
AMI = acute myocardial infarction; Blood lactate = mean blood lactate for group I and blood lactate obtained on the day that preceded shock development for group II; Coeff. = standardized canonical discriminant function coefficients; Corr. = pooled-within-group correlations between variables and canonical discriminant function; F1 = univariate F ratio; F2 = multivariate F ratio.

TABLE III Distribution of Various Values of Risk Index in Patients With and Without Cardiogenic Shock

	Group I			Group II		
Index	No. of Pts.	%	Cum. %	No. of Pts.	%	Cum. %
<−1	31	15	15	0	0	—
−1–0	106	50	65	3	18	18
0–1	55	26	91	3	18	35
1–2	18	8	99	2	12	47
2–3	2	1	100	3	18	65
>3	0	0	—	6	34	100

Cum. % = cumulative percent.

groups are shown in Figure 1. Although there was a rather wide variation of individual results in group II, 60% of patients in this group had blood lactate levels >3.6 mmol/liter on the day preceding the appearance of shock. Other variables (diabetes mellitus, blood creatinine, cardiac enzymes) were not found to have significant discriminating power, and there was no difference in proportions of patients with Killip class I or II between 2 groups. Regarding thrombolytic therapy, there was no significant difference between 2 groups either in the incidence of its administration or in the blood lactate concentrations between those who did and did not receive this treatment. We did not identify any possible extracardiac causes for hyperlactatemia.[6,7] All patients with non-Q-wave AMI were in group I, and there was no difference between their lactate levels and those of patients with Q-wave AMI belonging to group I.

With use of stepwise discriminant analysis, the following function for risk index (I) was computed: $I = 0.64 \times L + 0.174 \times U + 0.81 \times PI + 0.711 \times RTG + 0.387 \times A - 3.61$ where L = blood lactate (mmol/liter, mean value for group I, and the value obtained on the day before shock appearance for group II); U = peak blood urea (mmol/liter); PI = previous infarction (0 = no, 1 = yes); RTG = cardiomegaly on chest x-ray (0 = cardiothoracic ratio of <60%, 1 = cardiothoracic ratio of ≥60%); and A = age (0 = age <60 years, 1 = age ≥60 years).

The function had highly significant discriminating power: chi-square = 82, p <0.001. Discriminant function coefficients, correlations between variables and discriminant function, and F ratios are listed in Table II. The variable with the greatest predictive power was blood lactate concentration, followed by peak blood urea concentration. Previous AMI was also a significant predictor after adjusting for all other variables. X-ray cardiothoracic ratio and age did not achieve significant multivariate F ratio, but pooled-within-group correlations between these variables and canonical discriminant function were significant (>0.30). Inclusion of blood lactate into discriminant function analysis added significantly to the predictive power of the function: chi-square = 82 with lactate included versus chi-square = 54 when only other variables were entered into the analysis.

Distribution of various values of the risk index I in our study population is shown in Table III. The sensitivity, specificity and predictive value of the index I, taking various cutoff points, were analyzed. Using a cutoff level of 1, we found that I ≥1 detected 65% of patients who were to develop cardiogenic shock (sensitivity), and that the proportion of patients developing shock among those with I ≥1 was 36% (positive predictive value). A value of I <1 was observed in 91% of patients who did not develop shock (specificity), and correctly predicted hemodynamic stability in 97% of patients (negative predictive value). Taking a cutoff point of 2 resulted in a lower sensitivity (53%) but a high positive predictive value (82%); specificity and negative predictive value were very high (99 and 96%, respectively). Discriminant function was then validated in the second group of patients. In this group there were 56 patients that remained hemodynamically stable during their hospital stay (group I), whereas 6 patients developed cardiogenic shock (group II). The results of validation, considering the same cutoff points of the risk index, are highly consistent with those obtained from the study group: sensitivity 67%, specificity 88%, positive predictive value 36%, and negative predictive value 96% for a cutoff value of 1; and sensitivity 50%, specificity 98%, positive predictive value 75%, and negative predictive value 95% for a cutoff value of 2.

DISCUSSION

Many investigators have tried to identify high-risk patients with AMI and have described prognostic indexes using various clinical, biochemical, electrocardiographic, radiologic, invasive hemodynamic and radionuclide variables.[8–18] The study by Hands et al[19] focused specifically on prediction of shock development in patients with AMI using patients' age, left ventricular ejection fraction, serum creatine kinase, diabetes mellitus and history of previous AMI, and they found that shock occurrence could be predicted in >50% of cases. Although there is no evidence that early identification of high-risk patients would lead to a better prognosis, there is a theoretical possibility that early implementation of interventions, such as invasive hemodynamic monitoring or some new therapeutic modality, might decrease the incidence of manifest shock. As these interventions could be potentially hazardous, it would be important not to expose low-risk patients to the possible risk. The utility of such an index is even greater if it is based on simple clinical or laboratory findings that are

readily available for every patient. The value of peripheral blood lactate concentration as a predictor for new cardiac events has been demonstrated by Sheps,[1] and Kessler[2] and their associates, who have found it to be a useful prognostic marker for risk of recurrent cardiac arrest. Although the precise mechanism of elevated blood lactate is not clear, it could be related to peripheral tissue hypoperfusion.

In our study we found that blood lactate concentration is a significant predictor of shock development in patients with AMI, and that it can be used in conjunction with other simple clinical or laboratory data (patient's age, history of previous AMI, blood urea concentration and x-ray cardiothoracic ratio) to predict shock occurrence. Mean blood lactate concentration during the period from admission to the appearance of first clinical signs of shock was significantly higher in patients who developed shock (group II) than in patients who remained hemodynamically stable (group I). However, the difference was even greater and discrimination better when lactate value obtained on the day just preceding occurrence of shock in group II was compared with mean lactate concentration in group I (Table I). This value resulted in greater predictive power than any other variable included in the discrimination analysis (Table II). Figure 1 shows the daily lactate levels in the 2 groups; blood lactate in group II patients can be seen to increase 2 days before shock development, with further increase on the following day, demonstrating that the most recent value of blood lactate should be used for calculation of the risk index in everyday practice.

Despite significant univariate F ratios, cardiothoracic ratio and patients' age did not maintain statistical significance as multivariate predictors after adjustment was made for other variables (Table II). Nevertheless, we retained them in the analysis because of significant pooled-within-group correlations between them and canonical discriminant function, and because various studies have suggested that age[10,15,19–25] and heart size on x-ray[17] are important prognostic factors in AMI. Besides, regarding small number of patients with cardiogenic shock in our study, there is a greater tendency to a type II statistical error.

Our risk index for shock development exhibited a satisfactory potential for classifying patients with AMI who had no or only mild signs of left ventricular dysfunction (Killip class I and II) during early stages of AMI. With a cutoff value of 1 for the risk index, its sensitivity was 65% and specificity 91%, with positive predictive value 36% and negative predictive value 97%. With a cutoff point of 2, sensitivity was 53%, specificity 99%, positive predictive value 82% and negative predictive value 96%. These results are highly consistent with those obtained by cross validation of the function on the second group of patients.

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Long-Term Follow-Up of the First 56 Patients Treated with Intracoronary Self-Expanding Stents (The Lausanne Experience)

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Fifty-six patients treated with the self-expanding intracoronary stent for acute occlusion during percutaneous transluminal coronary angioplasty (PTCA) or restenosis were followed for 24 to 43 months (mean 34). Successful deployment and positioning were achieved in 55 of 56 patients. Occlusion of the stent was documented in 8 patients, the earliest occurring 30 minutes and the latest 8 months after implantation. Three of the occluded stents were recanalized by PTCA. Coronary artery bypass grafts (CABG) were required in 4 patients: 1 for symptomatic restenosis, 1 for left main stenosis adjacent to the stent and 2 for acute ischemia during the in-hospital stay (<7 days). Myocardial infarction occurred in the territory of the stented vessel in 8 patients. Seven patients died between 1 day and 19 months after implantation. Local bleeding complications occurred in 10 patients, with 5 requiring blood transfusion. Restenosis within the stent was angiographically documented in 5 patients (9%). A new lesion in the treated vessel was found in 10 patients, followed by implantation of a second stent in 5 and a third stent in 1 patient. Medical treatment was instituted in the remaining 4 patients. Forty-nine patients (88%) are alive. Twenty-nine patients (51%) remained asymptomatic, and 44 (78%) are in a better functional class than before the implantation. Eleven of 15 (79%) major complications (acute occlusions or deaths) occurred in patients who received a stent in the left anterior descending coronary artery. In conclusion, implantation of the self-expanding intracoronary stent appears to be a new therapeutic option for treating acute occlusion or restenosis after PTCA. However, stent occlusion remains an important limitation, and stents have to be significantly improved for use in small vessels.

(Am J Cardiol 1991;67:569–572)

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Acute coronary occlusion and chronic restenosis remain important limitations of percutaneous transluminal coronary balloon angioplasty (PTCA). Various mechanical[1–3] or thermal[4–7] devices have been developed in an effort to prevent acute occlusion and restenosis. Intravascular stents were developed as 1 potential approach to these problems.[8] However, currently available data suggest that thrombosis and reocclusion may also complicate stenting. We previously reported clinical data from patients treated[9–11] with the self-expanding stent (Wallstent™, Medinvent, S.A., Lausanne, Switzerland). The current study describes the long-term (≥2-year) incidence of restenosis and occlusion obtained from the first 56 consecutive patients treated with an intracoronary stent at the Centre Hospitalier Universitaire Vaudois.

METHODS

Three conditions were considered indications for implantation: (1) restenosis of a coronary artery after previous balloon angioplasty, (2) acute coronary occlusion after balloon angioplasty, and (3) stenosis of coronary artery bypass grafts (CABGs). The protocol was approved by our institutional ethics committee, and informed consent was obtained from each patient. The stent itself and the implantation technique have been described previously.[8] Briefly, calcium antagonists were given 1 hour before the procedure. Heparin (15,000 U) and aspirin (500 mg) were administered before implantation and the patients received 100,000 U of urokinase through the guiding catheter. After the implantation, acenocoumarol was begun. The target anticoagulation level was an international normalized ratio of >2.5. In addition, aspirin (250 to 500 mg/day), dipyridamole (150 to 300 mg/day) and calcium antagonists were administered. Sulfinpyrazone was also administered to the last 28 patients.

Patients: From April 1986 to December 1987, 56 patients with a mean age of 57 ± 9 years received 68 intracoronary stents. There were 49 men and 7 women. All had New York Heart Association functional class II to IV angina pectoris and 17 had previous CABGs. One-vessel coronary artery disease was present in 30 patients (54%), 2-vessel disease in 14 patients (25%) and 3-vessel disease in 12 patients (21%). The mean ejection fraction was 66 ± 11%. The left anterior descending coronary artery was the most frequent site of implantation, followed by the right coronary artery and CABG (Table I). Only stenoses >75% in diameter were at-

TABLE I Indications for Stenting and Localization of the Stents

Vessel	LAD	RCA	CX	CABG	D	Mam	Total
Restenosis	21	11	5	1	1	1	40
Occlusion	7	7	—	—	—	—	14
Primary stenosis	—	—	—	14	—	—	14
Total	28	18	5	15	1	1	68

CABG = coronary artery bypass graft; CX = circumflex coronary artery; D = diagonal coronary artery; LAD = left anterior descending coronary artery; Mam = mammary artery; RCA = right coronary artery.

tempted. The indication for stent implantation was post-PTCA restenosis in 59%, acute occlusion during PTCA in 20.5%, and stenosis of CABG in 20.5% of the patients. The size of the stents varied from 3.0 to 6.0 mm. The patients were discharged 4 to 20 days after implantation and followed up by their local referring physician or cardiologist. In all but 2 patients, a repeat coronary arteriogram was performed at least once 3 to 6 months after implantation or earlier if angina pectoris recurred. All patients were treated for ≥6 months with the following antithrombotic regimen: acenocoumarol, dipyridamole and sulfinpyrazone. After 6 months, only aspirin was continued. Angiographic restenosis was defined as a luminal reduction of ≥50%. Long-term follow-up data were obtained either from a questionnaire sent to the local physician or during clinic visits.

RESULTS

In-hospital follow-up (Figure 1): The deployment and correct positioning of the stent was successful in 55 patients (98%). In-hospital stay was unremarkable for 42 of 56 patients (75%).

Death: Two patients (4%) died during the acute hospital course. In 1 patient in cardiogenic shock, the stent was implanted after an acute left anterior descending coronary artery occlusion 40 minutes after PTCA.[10] Because of failure in x-ray equipment, the stent appeared to have been placed distal to the stenosis, but anterograde flow was excellent at the end of the procedure.

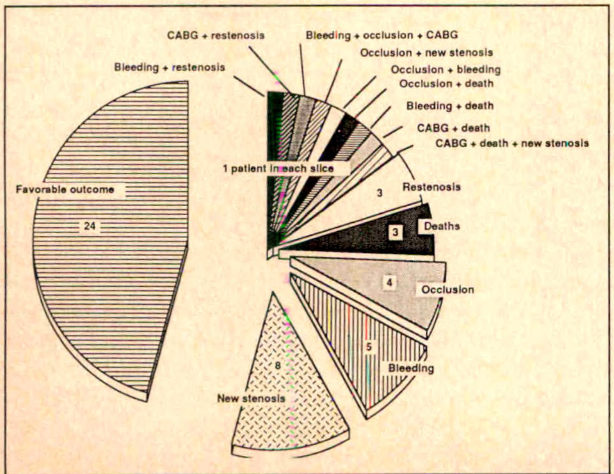

FIGURE 1. Follow-up data. CABG = coronary artery bypass graft; new stenosis = a stenosis proximal or distal to the stent not present at the time of implantation.

This patient died 16 hours after the procedure from intractable ventricular arrhythmias. Another patient with successful implantation developed acute myocardial ischemia shortly after a maximal stress test. He underwent successful coronary artery bypass grafting, but died 12 hours after the procedure, probably from tamponade.[8]

Occlusion: In-hospital stent occlusion occurred in 4 patients, 1 to 7 days after implantation. One silent occlusion was treated medically, and recanalization with balloon angioplasty and intracoronary thrombolysis was successfully achieved in the other 3 patients. One of these 3 underwent successful surgical revascularization for subsequent ischemic episodes. After correction of a false aneurysm of the femoral artery, 1 patient had an acute occlusion of the endoprosthesis 3 months after implantation. Myocardial infarction was documented in all 4 patients with a significant increase in creatine kinase levels.

Minor complications: Minor complications also occurred, with bleeding at the femoral puncture site in 8 patients. Five required surgical repair. During the hemorrhagic event, 1 patient had an acute occlusion of the endoprosthesis. He underwent successful PTCA/recanalization, but as angina pectoris recurred 2 days later, coronary artery bypass grafting was performed, without any further problems.

Long-term follow-up (Figure 1): Thirty-four ± 6 months after stent implantation, 44 patients (79%) were in a better functional stage than before. Thirty-four patients (61%) had no new cardiac events during that period.

Death: A total of 5 patients died during follow-up (9%). One patient was admitted in ventricular fibrillation 1 week after the left anterior descending coronary artery was stented. Anterior myocardial ischemia was present on an electrocardiogram before admission. No autopsy was performed, and it later appeared that the patient was not correctly anticoagulated.[9] The second patient had documented stent occlusion on angiography performed 6 months after implantation; he died suddenly at 19 months. The third patient presented with an anterior myocardial infarction 2 months after implantation of a stent in the left anterior descending coronary artery and died from electromechanical dissociation (his anticoagulation had been stopped by his referring physician). The fourth patient died from cardiogenic shock 7 months after the implantation of a stent in a CABG.[11] He had severe 3-vessel disease, with severe left ventricular dysfunction at the time of the implantation. In the fifth patient, death was from cardiogenic shock after cardiac surgery performed for unstable angina pectoris secondary to severe stenosis of the left main coronary artery. The stent had been placed 3 months earlier in the proximal left anterior descending coronary artery and was found to be patent. Myocardial infarction occurred in 6 patients. In 3 of these, stent occlusion had been documented by angiography. The 3 other patients died.

New angiographic lesions: In 10 patients (18%), a new stenosis in the stented vessel was present at repeat

angiography performed 3 to 6 months after implantation. This stenosis was immediately adjacent to the prosthesis in 4 patients. In 6 patients, a new stent was implanted for recurrence of angina. One patient underwent PTCA of the left anterior descending coronary artery for a 75% stenosis distal to the stent. Two patients received medical therapy as sole treatment. During follow-up, an occlusion of the stented vessel was documented angiographically in 4 patients but no recanalization was attempted in 3 patients. Minor problems, such as bleeding, occurred in 1 patient at the femoral puncture.

Restenosis: Angiographic restenosis was documented in 5 patients (9%); 2 had a stent placed in the left anterior descending coronary artery; 1 who was asymptomatic had a stent placed in the right coronary artery; and 2 had a stent placed in a venous CABG. Three patients were treated medically, 1 underwent coronary artery bypass grafting and 1 underwent coronary atherectomy followed by excimer laser angiography without permanent success.

Discussion: A number of new ways are currently being developed to improve the long-term outcome of PTCA, among them intracoronary stenting. Despite reports of excellent short-term safety and efficiency,[9,10] no prospective studies have been performed that compare restenosis rates after PTCA alone with those after PTCA and implantation of endoluminal support devices. Also, the time course of the development of significant intraluminal tissue ingrowth within stents is not well understood in humans.

From our retrospective analysis of the first 56 patients who had intraluminal self-expanding stents implanted for documented restenosis, abrupt closure after angioplasty and restenosis or significant first stenosis, CABG restenosis is a rare phenomenon. When compared with restenosis rates obtained from other studies,[12-14] the restenosis rate in patients with self-expanding intracoronary stents seems to be much lower, i.e. 9% versus the expected >30%. The true restenosis rate is only available for the first 6 months in our group of patients, because only symptomatic patients underwent repeat angiography after this time. However, the likelihood of late occlusion or restenosis in asymptomatic patients is low. Symptomatic and asymptomatic restenosis was angiographically documented in only 5 patients (9%).

The analysis of tissue samples obtained from directional atherectomy seems to indicate that restenosis is primarily due to smooth muscle proliferation. Whether the lower incidence of restenosis after stenting with self-expanding coronary stents is related to a lesser degree of fibromuscular proliferation or to an optimally enlarged primary lumen, allowing for certain degrees of intimal hypoplasia without flow reduction, is still unclear. Empirically, in patients with suboptimal PTCA results, restenosis is more frequent.[15] The stimulus responsible for smooth muscle cell proliferation has yet to be identified; either flow turbulence due to intimal fissures, plaque rupture or the presence of residual lesions may well be 1 of the stimuli promoting fibromuscular ingrowth. Consequently, reduction of turbulent flow as the result of an increase in luminal diameter and elimination of wall irregularities may well be 1 of the key factors responsible for the lower number of restenoses after stenting. Self-expanding stents, which tend to produce luminal diameter increments even after the initial procedure, would seem to be particularly suitable for this purpose. This mechanism is counterbalanced by the possible chronic stimulation of cellular proliferation by the presence of a foreign body. New lesions in the stented vessels occurred in 18% of our patients, a percentage not different from that observed by others, where new lesions occurred in 20 to 25% of patients after PTCA alone.[16] The initial acute complication rate after stenting with self-expanding stents was in the order of 10% in this initial series. This is significantly higher than that seen with balloon angioplasty alone. It must be pointed out, however, that this report deals with high-risk patients, and that angioplasty and bypass surgery were considered contraindicated for a number of them. When stents are used to treat PTCA complications, the risk analysis of stent implantation should be compared with the mortality rate (up to 15%)[17] and the high incidence of myocardial infarction (31 and 71%)[17] of emergency coronary surgery. The overall mortality of the first 56 patients with intracoronary stents was higher than expected with PTCA alone.[12,13] It is interesting to note that all patients who died had a stent positioned in the left anterior descending coronary artery, except 1; this patient had bypass graft stenting in the presence of 3-vessel disease with poor left ventricular function and died from cardiogenic shock. The association between small vessel size and complications is also striking. Stent occlusions in this series occurred despite considerable effort to maintain a heavy anticoagulant regimen with the potential and documented increase in bleeding complications.

Clinical implications: Recommendations for the use of self-expanding stents in coronary arteries or bypass grafts should include strict patient selection. Bypass grafts >4 mm, in which stents of ≥4.5 mm in diameter can be implanted, are excellent targets for stent implantation and will in the majority of cases provide satisfying long-term results. Bail-out situations in >3.5-mm vessels are equally acceptable substrates for implantation of self-expanding stents. However, elective surgical revascularization should be strongly considered in the patients treated with the self-expanding stent for acute occlusion after PTCA. In medium- or small-sized left anterior descending coronary arteries, self-expanding stents of the first generation cannot be recommended. Implantation of self-expanding stents for recurrent restenosis in large native coronary arteries requires further investigation, because, despite heavy anticoagulation, the complication rate is still too high with this first-generation device. Improvement of stent design and surface coating may enlarge the indication for implantation of endoluminal support devices.

Acknowledgment: We thank Michael Ziles, MD, for help in the preparation of this manuscript.

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Capabilities of Supine Exercise Electrocardiography Versus Exercise Radionuclide Angiography in Predicting Coronary Events

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The ability of supine exercise electrocardiography and exercise radionuclide angiography to predict time to subsequent cardiac events (cardiac death, nonfatal myocardial infarction or late coronary bypass grafting or angioplasty) were compared in 265 patients with normal resting electrocardiograms who were not taking digoxin. All patients had undergone coronary catheterization and were initially treated medically. Follow-up study was performed at a median of 51 months. Separate logistic regression models, which had been previously developed to predict 3-vessel or left main coronary artery disease (CAD), were compared using a Cox regression analysis to predict time to a subsequent cardiac event. The exercise electrocardiography model, consisting of the magnitude of ST depression, exercise heart rate and patient gender, was a powerful predictor (chi-square = 30.8, p <0.0001) of subsequent events. The exercise radionuclide angiography model, which included the exercise response of the pressure-volume ratio in addition to the exercise electrocardiography variables, had similar prognostic power (chi-square = 31.8, p <0.0001). In a separate analysis considering only cardiac death and nonfatal myocardial infarction, the exercise electrocardiography model remained a significant predictor of events (chi-square = 12.2, p <0.001). None of the radionuclide angiography variables added significantly to the prognostic power of the exercise electrocardiography model. Thus, in patients with a normal resting electrocardiogram who are not taking digoxin, the supine exercise electrocardiography model that predicts 3-vessel or left main CAD also predicts future cardiac events. Exercise radionuclide angiography does not provide any additional prognostic information in such patients.

(Am J Cardiol 1991;67:573–577)

From the Mayo Clinic and Foundation, Rochester, Minnesota. Manuscript received October 11, 1990; revised manuscript received and accepted November 13, 1990.

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Exercise electrocardiography can identify patients with severe (left main or 3-vessel) coronary artery disease (CAD),[1,2] patients at high risk for future cardiac events,[3] and patients more likely to benefit from treatment with bypass surgery.[4] Exercise radionuclide angiography can also be useful for these purposes.[5–11] Although exercise radionuclide angiography has been shown to be superior to exercise electrocardiography in diagnosing CAD,[12–14] few studies have compared exercise radionuclide angiography and exercise electrocardiography for the purposes of identifying severe CAD or predicting patient outcome. A recent comparison of these techniques in patients with a normal resting electrocardiogram who were not taking digoxin[15] determined that exercise radionuclide angiography added very little incremental information for the identification of severe CAD. The current study compares the prognostic value of exercise electrocardiography and exercise radionuclide angiography in the subset of patients from the aforementioned study[15] who were subsequently treated with initial medical therapy.

METHODS

Patients: The study group consisted of a consecutive series of patients with known or suspected CAD who underwent rest and supine exercise radionuclide angiography and coronary angiography within 6 months of the exercise radionuclide angiography and without evidence of an intervening cardiac event. Reasons for exclusion included: (1) previous coronary revascularization by either coronary artery bypass grafting or coronary angioplasty; (2) hemodynamically significant valvular heart disease; (3) any abnormality (other than sinus bradycardia) on the resting electrocardiogram; and (4) digoxin therapy. Of the 408 patients who met these criteria, 391 had complete data at the time of the previous analysis.[15] One hundred nineteen of these 408 patients underwent bypass surgery or angioplasty within 30 days of cardiac catheterization and were excluded from this analysis. These patients had a higher incidence of prior myocardial infarction, worse symptoms, poorer exercise performance, and more extensive CAD than the 289 patients who were treated initially with medical therapy (Table I). Of the 289 patients, 6 had missing exercise data and 18 were lost to follow-up and were excluded

TABLE I Comparison of Patients Treated with Initial Medical Therapy Versus Revascularization

Variable	Initial Medical (n = 289)	Initial Revascularization (n = 119)	Chi-Square*
Clinical			
Age (mean), years	56	58	5.01
Male gender (%)	173 (60)	94 (79)	15.01
Prior myocardial infarction (%)	29 (10)	24 (20)	5.14
Typical angina (%)	129 (45)	99 (83)	28.77
New York Heart Association class			
0–2 (% of typical)	78 (60)	48 (48)	
3–4 (% of typical)	51 (40)	51 (52)	
Exercise testing			
Exercise work load (median), kg-m/min	600	600	3.92
Exercise heart rate (median), beats/min	126	112	12.58
Exercise heart rate × blood pressure (median)	22,608	19,032	19.81
Angina during test (%)	42 (15)	33 (28)	11.17
Positive electrocardiogram (%)	138 (48)	85 (71)	35.65†
Rest ejection fraction (mean), %	61	60	1.45
Exercise ejection fraction (mean), %	59	54	13.62
Change in ejection fraction (exercise–rest), %	−2	−6	11.60
Worsening wall motion during exercise			
0 Walls (%)	196 (68)	47 (40)	28.75
1 Wall (%)	77 (26)	49 (41)	
2 Walls (%)	14 (5)	22 (18)	
3 Walls (%)	2 (1)	1 (1)	
Number of coronary arteries narrowed >70% in diameter			
0 (%)	149 (52)	0 (0)	114.31
1 (%)	65 (22)	27 (23)	
2 (%)	48 (17)	39 (33)	
3 (%)	27 (9)	53 (44)	

* Chi-square values on 1 degree of freedom for entry into logistic regression model with initial therapy (medical versus revascularization) as the dependent variable. Chi-square values >3.84 correspond to p <0.05, >6.63 to p <0.01, and >10.8 to p <0.001, and indicate the significance of the association for a given variable with revascularization.
† Chi-square value corresponds to this variable coded as to degree of ST-segment depression.
Numbers in parentheses refer to percentages of patient group.

from analysis. The remaining 265 patients constitute the study group.

Exercise protocol and radionuclide angiography: Resting electrocardiography and supine bicycle ergometry with exercise electrocardiography were performed and interpreted as previously described.[15] Red blood cell labeling was performed with 30 mCi of technetium-99m using the in vivo[16] or modified in vivo procedure.[17] Radionuclide angiograms were obtained at rest and during exercise and processed and analyzed, including determination of cardiac volumes, calculation of ejection fraction and assessment of regional wall motion, as previously described.[15,18–20] The pressure-volume ratio was defined as the ratio of the systolic blood pressure to the end-systolic volume. The exercise response of the pressure-volume ratio was calculated using the definition of Dehmer et al[21]: exercise response of pressure-volume ratio = (exercise systolic pressure × rest end-systolic volume)/(exercise end-systolic volume × rest systolic pressure).

Coronary angiography: Coronary angiography was performed as previously described.[15] Lesions were classified as significant using the definitions of the Coronary Artery Surgery Study.[22]

Follow-up: Follow-up data were obtained by chart review or patient contact. Significant events were defined as cardiac death, nonfatal myocardial infarction, and coronary artery bypass grafting or coronary angioplasty >3 months after catheterization. Late revascularization has been included in other studies as a proxy for worsening disease.[23–25] To exclude such patients underestimates the actual event rate, whereas including them overestimates the rate. Although the initial noninvasive testing may have influenced late revascularization, it is unlikely that this occurred, given the median time to revascularization of 15 months (twenty-fifth percentile 189 days, seventy-fifth percentile 1,025 days). In fact, 19 of the 24 patients (79%) who underwent late revascularization were hospitalized for clinical deterioration before surgery or angioplasty. A separate analysis of cardiac death and nonfatal myocardial infarction only was also performed.

Statistical analysis: In a previous study[15] a logistic regression analysis was used to determine which clinical and exercise test variables were significantly associated with severe CAD, and to develop models to predict the presence or absence of severe CAD. The exercise electrocardiography model included gender, magnitude of ST-segment depression and exercise heart rate. The exercise radionuclide angiography model included these same 3 variables as well as the exercise response of the pressure-volume ratio. The exercise response of the pressure-volume ratio was the only exercise radionuclide angiography variable that significantly increased the ability of the exercise electrocardiography model to identify severe CAD. These 2 models were then used to

TABLE II Univariate Significance of Clinical and Exercise Variables in Patients with Events

Variable	Patients Without Events (n = 227)	Patients With Events (n = 38)	Chi-Square*
Age (mean), years	56	56	0.48
Male gender (%)	127 (56)	29 (76)	7.22
Previous myocardial infarction (%)	23 (10)	3 (8)	0.06
Exercise work load (median), kg-m/min	600	600	0.67
Exercise heart rate (median), beats/min	128	114	10.62
Positive exercise electrocardiogram (%)	105 (46)	27 (71)	8.02†
Exercise response of the pressure-volume ratio (median)‡	1.21	1.06	2.52
Exercise ejection fraction (mean), %	60	57	0.66
Change in ejection fraction (exercise–rest), %	−1	−3	0.05
Exercise left ventricular end-systolic volume index (median), ml/m²	40	42	1.16
Exercise wall motion score (median)§	3.0	3.5	3.46
Worsening wall motion during exercise			
0 Walls (%)	162 (71)	19 (50)	4.88
1 Wall (%)	54 (24)	16 (42)	
2 Walls (%)	10 (4)	2 (5)	
3 Walls (%)	1 (1)	1 (3)	

* Chi-square values at first step in proportional hazards regression analysis assessing the association between these variables and time to a cardiac event. Chi-square values >3.84 correspond to p <0.05, >6.63 to p <0.01, and >10.8 to p <0.001.
† Chi-square value corresponds to this variable coded as to degree of ST-segment depression.
‡ Refer to text for definition.
§ The average of scores for 3 segments (septal, inferoapical, lateral) using a 6-point grading system (1 = normal, 2 = mild hypokinesia, 3 = moderate hypokinesia, 4 = severe hypokinesia, 5 = akinesia, 6 = dyskinesia).
Numbers in parentheses refer to percentages of patient group.

separate the study population into subgroups of low, intermediate and high probability of severe CAD. In the current study, each of the original sets of variables were compared using a Cox regression analysis to predict time to a subsequent cardiac event. Other exercise radionuclide angiography variables were also examined to determine if they added significant incremental prognostic value to the exercise electrocardiography model. Event-free survival curves for subgroups of patients identified as low, intermediate and high probability of severe CAD on the basis of the exercise electrocardiography and exercise radionuclide angiography models were estimated by the Kaplan-Meier method.[26]

RESULTS

Events: Median time to follow-up was 51 months (range 3 to 78). During follow-up 38 patients had initial cardiac events: 6 cardiac deaths, 8 nonfatal myocardial infarctions and 24 late revascularizations. Patients with events were more likely to be men and to have a positive electrocardiogram, a lower peak heart rate, and more deterioration in wall motion during exercise (Table II).

Of the 38 patients with events, 13 had 3-vessel, 11 had 2-vessel and 10 had 1-vessel CAD. Four patients had no significant CAD (3 had coronary artery lesions ≤60% and 1 had clinically unsuspected aortic stenosis).

Prognostic capabilities of the models: The exercise electrocardiography model was significantly predictive of subsequent cardiac events (chi-square = 30.8, p <0.0001). Each of the 3 variables was significantly associated with time to an event after adjustment for the other 2 variables (magnitude of ST depression - chi-square = 16.0, p <0.0001; peak heart rate - chi-square = 13.5, p <0.001; male gender - chi-square = 5.9, p <0.02). The exercise radionuclide angiography model was also predictive of subsequent cardiac events (chi-square = 31.8, p <0.0001). However, the only radionuclide angiography variable included in the model, the exercise response of the pressure-volume ratio, was not significantly associated with future events after adjustment for the 3 exercise electrocardiography variables (chi-square = 1.8, p = 0.18). In addition, none of the other radionuclide angiography variables listed in Table II added any significant prognostic information to the exercise electrocardiography model. The greatest chi-square for any variable was for worsening wall motion during exercise (chi-square = 1.96, p = 0.16).

When late revascularization was included as an end point, there were no differences in event-free survival for any of the patient subgroups (predicted to have low, intermediate or high probability of severe CAD) using the exercise electrocardiography versus the exercise radionuclide angiography models (Figure 1). In a separate analysis that considered only death and myocardial infarction as end points, the exercise electrocardiography model was still significantly, although not as strongly, predictive of events (chi-square = 12.2, p <0.001). None of the exercise radionuclide angiography variables added any significant prognostic information to the exercise electrocardiography model. Again there were no differences in event-free survival within patient subgroups predicted to have low, intermediate or high probability of severe CAD using the 2 models (Figure 2).

DISCUSSION

A previous report[15] showed that exercise radionuclide angiography adds very little information to exercise electrocardiography for the accurate identification of severe CAD in patients with a normal resting electrocardiogram who were not taking digoxin. The current study shows that exercise radionuclide angiography also does not add any prognostic information to exercise

electrocardiography for this subset of patients who were treated initially with medical therapy. Because this study used the same 2 models that were previously described,[15] the clinician is provided with a simple and practical exercise electrocardiography model that can predict the likelihood of both severe CAD and subsequent cardiac events.

Several previous studies have demonstrated the prognostic utility of exercise radionuclide angiography in patients with CAD.[5-11] However, these previous studies probably included many patients with resting electrocardiographic abnormalities or left ventricular dysfunction, or both, since these were not criteria for exclusion in these studies. The current study was restricted to patients with chest pain and normal resting electrocardiograms who were not taking digoxin. In a community-based population, 60% of patients initially presenting with angina pectoris fulfilled these criteria.[27] Exercise electrocardiography is more specific in the absence of resting electrocardiographic abnormalities and digoxin use.[28] A previous report from our laboratory demonstrated that 95% of patients presenting with chest pain and a normal resting electrocardiogram (who were not taking β blockers) had a normal resting ejection fraction in the absence of a history of myocardial infarction.[29] In fact, 92% of the patients in this study (19% of whom were taking β blockers) had an ejection fraction $\geq$50%. In such patients with normal left ventricular function, the major determinants of outcome are the extent of CAD and the severity of exercise-induced ischemia. This study indicates that exercise electrocardiography provides adequate prognostic information, presumably because it effectively screens for these variables.

Few studies have examined the incremental prognostic value of exercise radionuclide angiography compared with exercise electrocardiography in this setting. Ladenheim et al[30] reported results of exercise electrocardiography and thallium scintigraphy in 1,451 patients with normal resting electrocardiograms. Exercise thallium scintigraphy failed to significantly increase the ability of clinical and exercise electrocardiography variables to predict cardiac event rates during 1 year of follow-up. Using exercise radionuclide angiography, and with longer follow-up, our results are similar.

We have previously described the limitations of this type of study.[15] The most important limitation is patient selection bias. The original study patients[15] consisted of a referral population undergoing evaluation at a tertiary medical center. All underwent coronary angiography.

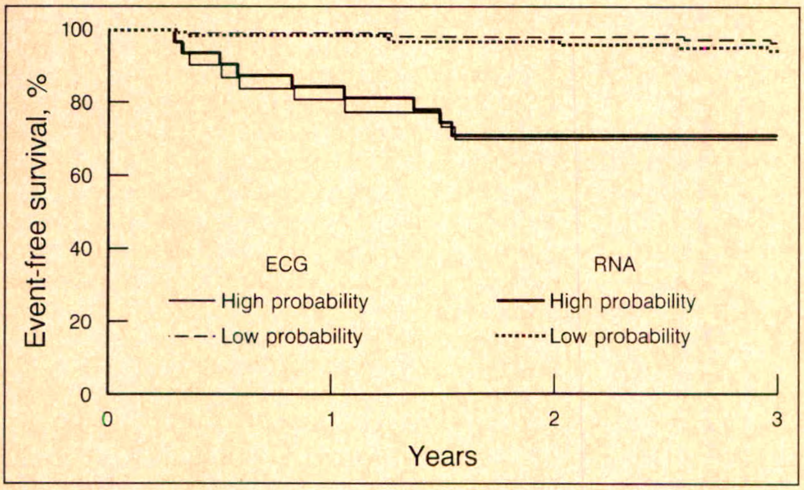

FIGURE 1. Survival free of all events (cardiac death, nonfatal myocardial infarction and late revascularization) for patient subgroups predicted to have a low or a high probability of severe coronary artery disease using the exercise electrocardiography (ECG) model and the exercise radionuclide angiography (RNA) model.

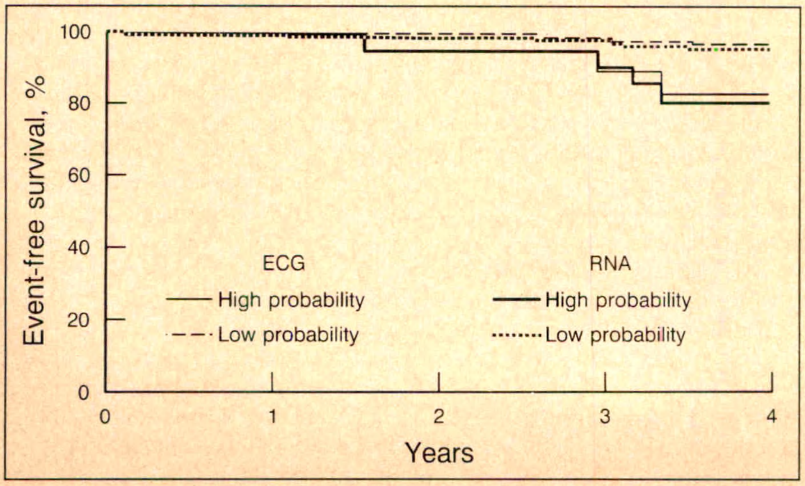

FIGURE 2. Survival free of hard events (cardiac death and nonfatal myocardial infarction only) for patient subgroups predicted to have a low or a high probability of severe coronary artery disease using the exercise electrocardiography (ECG) model and the exercise radionuclide angiography (RNA) model.

The current study population is even more highly selected because 29% of the original patient population were treated with early revascularization and therefore excluded from the current analysis. The patients treated with early revascularization had more severe clinical and angiographic CAD (Table I), and presumably would have had a higher event rate than those treated medically. The results of this study need to be confirmed in other patient groups, both from other referral centers and from community-based populations that have not undergone cardiac catheterization, before they can be widely applied.

Acknowledgment: We thank Tammy Hudson for assistance in obtaining follow-up information on these patients and Shelly O'Groske for secretarial support in the preparation of this manuscript.

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Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (The CASCADE Study)

The CASCADE Investigators*

This randomized study evaluates survivors of out-of-hospital ventricular fibrillation (VF) not associated with a Q-wave acute myocardial infarction who are deemed to be at a high risk of recurrence of VF. It compares the outcome of treatment with empirically administered amiodarone with the outcome of treatment with other antiarrhythmic agents guided by electrophysiologic testing or Holter recording, or both. The goal of therapy guided by electrophysiologic testing is to suppress inducible ventricular tachycardia (VT) or VF. Holter recording is used as the primary means of adjusting therapy only if patients are noninducible at the baseline electrophysiologic study. Patients are stratified according to cardiac diagnosis, ejection fraction, and whether they had previously received an antiarrhythmic agent that failed to suppress their arrhythmias. The primary end point of the study is total cardiac mortality.

The first patient was enrolled in a pilot study on April 26, 1984. By October 1988, 142 patients had been enrolled in the full study and, as of May 1990, 199 patients have been enrolled. Compliance with therapy has been good, with no patients lost to follow-up and 8% of patients, equal in both drug groups, crossing over to alternate therapy. Baseline clinical characteristics remain similar in amiodarone and conventional drug groups. Pulmonary toxicity with amiodarone is 7% at 1 year, with no patients dying of pulmonary toxicity. In the first 142 patients, the overall 1-year cardiac mortality was 19%, with a 17% arrhythmic mortality (either VF or presumed arrhythmic death). Because of this relatively high mortality, even with aggressive evaluation, treatment and follow-up, the investigators concluded that all patients who were participants in the study should also have an automatic defibrillator implanted when possible. Enrollment will continue until March 31, 1991, with follow-up for an additional year thereafter. This study should provide data about the relative efficacy of empirically administered amiodarone compared with other antiarrhythmic agents guided by electrophysiologic study and Holter monitoring.

(Am J Cardiol 1991;67:578–584)

Patients who are resuscitated from an episode of out-of-hospital cardiac arrest remain at risk of recurrence of cardiac arrest.[1,2] Particularly high-risk patients can be identified, as well as patients for whom the risk of recurrent cardiac arrest is low.[3,4] The impact of antiarrhythmic drug therapy on prevention of the recurrence of cardiac arrest in moderate- to high-risk patients is unknown.[5,6]

Some studies have concentrated on patients with recurrent sustained ventricular tachycardia (VT) who are thought to have the substrate for out-of-hospital cardiac arrest.[7,8] Our patients with out-of-hospital ventricular fibrillation (VF) differ from patients with recurrent sustained VT,[9,10] although it has been suggested that many episodes of VF may be preceded by at least a few seconds of a more organized VT before the arrhythmia degenerates into VF. In Seattle, however, sustained VT is rarely identified in cases of out-of-hospital cardiac arrest.[11] The present study examines only patients who have had documented out-of-hospital VF.

The Seattle experience is often used as the basis of comparison for other studies because its scope is community-wide and is a large population of patients who have been resuscitated from VF.[1–4] A relatively high success rate of resuscitation is attributable to the high incidence of bystander cardiopulmonary resuscitation, the rapid arrival time of the first responders and paramedics, and early defibrillation attempts.[12]

Because of these factors, a substantial number of patients have become long-term survivors of out-of-hospital VF in Seattle (57 to 117 per year). These patients provide an opportunity to evaluate clinical, epidemiologic and therapeutic factors responsible for subsequent cardiac mortality and morbidity.

Although it is unknown if any antiarrhythmic drug prevents VF, it has been the standard of practice in recent years to treat most high-risk patients with antiarrhythmic drug therapy. Because of this prevailing opin-

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ion, it has not been possible to compare drug therapy with placebo. Furthermore, amiodarone has been considered to be an effective agent for potentially fatal ventricular arrhythmias.[13] Whether it is superior to other antiarrhythmic agents, however, is not known. Because of its long half-life, amiodarone can be administered simply as a once-daily dosage; however, adverse effects are frequent.[14] The present study compares amiodarone, as an empirically administered antiarrhythmic agent, to other antiarrhythmic agents guided by electrophysiologic testing and Holter recording. This article outlines the experimental protocol and describes preliminary results.

METHODS

Two sources provide patients for this study: (1) primary events attended by the Medic I paramedic system, and (2) tertiary referral from other cities. Medical reports are completed and filed centrally for all patients attended by Seattle's Medic I system. Reports of patients with cardiac arrest are generally available within 48 hours after the event. Reports of all patients whose initial cardiac rhythm was VF are reviewed by the Medic I administrative personnel and forwarded to the coordinators of the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) study. Between 200 and 300 cardiac arrests occur in Seattle each year, and approximately one-quarter to one-third of patients are discharged alive. Thus, some 50 to 100 patients per year survive an episode of VF and recover sufficiently to be considered candidates for this study.[15] Patients are evaluated at the hospitals to which they were admitted and assessed for risk of recurrence of VF. Patients for whom the risk of recurrent VF is estimated to be ≥20% in 1 year (primarily patients who have not had a Q-wave myocardial infarction with the episode of VF) are considered study candidates. Risk factors for recurrence of VF are male sex, a remote myocardial infarction, a history of remote congestive heart failure or depressed left ventricular ejection fraction, no new Q-wave myocardial infarction with the VF,[3,4] frequent or complex arrhythmias on Holter recording, or both,[16] inducibility at electrophysiologic testing,[17] and advanced age.[18] Patients are approached for this study as soon as they are stable and have recovered neurologically, up to a maximum of 6 months from the VF episode. After 6 months, patients are no longer eligible. Study candidates undergo a baseline drug-free Holter recording and an electrophysiologic study. If they have clinical factors that predict a moderate to high risk of VF recurrence and have either inducible VT or VF at electrophysiologic study[9] or complex arrhythmias on Holter monitoring, or both, they are considered candidates for the study and are approached by 1 of the principal investigators or nurse coordinators. Patients who agree to enrollment are then randomized either to empiric amiodarone therapy or to therapy with other antiarrhythmic agents guided by invasive electrophysiologic testing or Holter recording (Figure 1). Randomization occurs after surgery if patients are to be referred for any cardiac surgical procedure. Patients are stratified according to the presence or absence of coronary artery disease, ejection fraction >0.30 or ≤0.30, and presence or absence of prior drug failure. Drug failure is defined either as (1) spontaneous sustained arrhythmia recurrence with acceptable therapeutic levels of antiarrhythmic drugs (either before or after the VF episode), or (2) inducible sustained ventricular tachyarrhythmias at electrophysiologic study with acceptable therapeutic levels of antiarrhythmic drugs. After randomization, patients assigned to the amiodarone arm receive amiodarone "loading," initially 1,200 mg/day for up to 10 days and then 200 to 800 mg (mean 600) orally once a day for 1 to 2 months, depending on drug tolerance. Doses are then tapered to a maintenance dose of 100 to 400 mg/day. Patients randomized to conventional therapy guided by electrophysiologic testing receive procainamide, quinidine, disopyramide, tocainide, mexiletine, encainide, flecainide, propafenone, or combination therapy, in that order, in doses that achieve predicted therapeutic serum levels, and omitting drugs previously ineffective or that have caused intolerable adverse effects. Table I outlines the experimental protocol.

Successful suppression of arrhythmias is considered to be suppression of inducible sustained VT or VF. Waller et al[19] suggested that slowing of the induced VT rate is also a reasonable measure of adequate protection from an antiarrhythmic drug used to prevent cardiac mortality, and slowing of the induced VT cycle length by ≥100 ms was accepted in our protocol as an adequate end point, if complete suppression of inducible VT could not be accomplished with any antiarrhythmic drug tried. Only if no suppression or slowing of inducible VT could be accomplished with any drug or combination would a patient be crossed over to amiodarone therapy.

Patients noninducible at the baseline electrophysiologic study (or who did not undergo electrophysiologic study for other reasons) but with frequent or complex arrhythmias (couplets or ventricular tachycardia), or

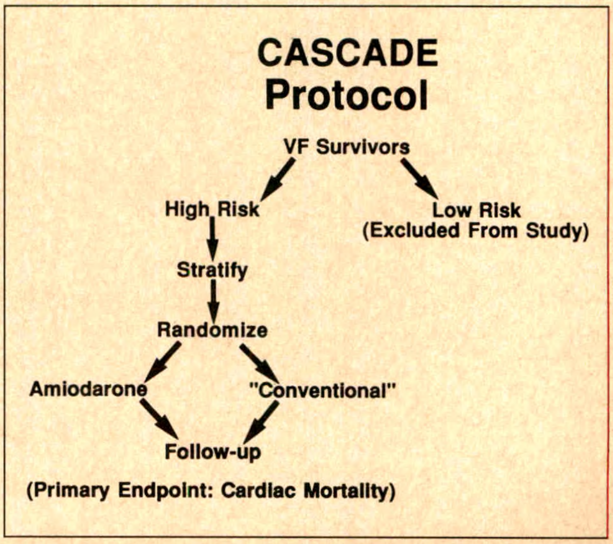

FIGURE 1. Protocol for Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) study. High-risk patients who have survived an episode of ventricular fibrillation (VF) are stratified and randomized to receive either empiric amiodarone or therapy with other antiarrhythmic agents guided by electrophysiologic testing.

TABLE I Outline of Protocol

	Baseline	1 Month	3 Months	6 Months	12, 24, 36 Months
History, physical exam	XO	XO	XO	XO	XO
Electrocardiogram	XO	XO	XO	XO	XO*
Chest x-ray	XO				O
Serum levels for antiarrhythmic drug	X with drug	X	X	X	X
Holter recording	XO	XO	XO	XO	XO
Electrophysiologic study	XO X with drug				
Electrolytes/complete blood count	XO				
Radionuclide ventriculogram	XO				
Slit lamp exam	O		O	O	O
Thyroid-stimulating hormone	O		O	O	O
Diffusing capacity	O		O		O
Quality of life questionnaire	XO			XO	XO*

* At 12, 18, 24, 30 and 36 months.
O = amiodarone therapy; X = conventional therapy.

both, on Holter recording have drugs and dosages adjusted based on response determined by Holter recording. Successful suppression of Holter ectopy was considered to be ≥70% suppression of ventricular premature complexes and ≥90% suppression of runs of VT.[20] Patients who have neither a positive electrophysiologic study nor complex arrhythmias on Holter monitoring are not included in this study, because of the absence of a marker for adjustment of therapy for antiarrhythmic drugs.

End points, statistics and data analysis: Because of the difficulty and potential bias in assigning the cause of death (arrhythmic vs nonarrhythmic) to patients in this study,[21] and because the study is not blinded with respect to the drug assignment, the primary end point of the study is total cardiac mortality. Total cardiac mortality is an end point difficult to misclassify and includes sudden arrhythmic cardiac deaths, documented resuscitated out-of-hospital VF, and nonarrhythmic cardiac death. Patients are also considered to have reached the primary end point if they have a documented episode of out-of-hospital cardiac arrest with VF (but not VT) from which they are resuscitated. Secondary end points to be evaluated are arrhythmic mortality (including patients resuscitated from documented VF), total mortality, nonarrhythmic cardiac death, total arrhythmia recurrence (including sustained VT), ventricular ectopic activity and VT on Holter monitoring, adverse effects, length of hospital stay, cost of therapy, ease of therapy, quality of life, rehospitalization rates, compliance, cessation of therapy, crossing over to alternate therapy, and loss of patients to follow-up. Patients are analyzed by intention to treat, remaining in their randomization group even if they discontinue the drug or cross over to the alternate therapy.

At the time of the study design (1982), the automatic implantable cardioverter/defibrillator was not commonly used because it was still experimental,[22] and it was expected to have only a minor impact on this study. Nevertheless, other end points had to be defined before the initiation of the study for patients in whom an automatic implantable cardioverter/defibrillator was used. We arbitrarily defined a syncopal episode followed by an automatic defibrillator shock as the equivalent of a cardiac arrest and therefore a qualifying primary end point for this study. Symptoms of dizziness, dyspnea, palpitations or near-syncope followed by an automatic defibrillator shock would not be counted as an episode of VF, and an automatic defibrillator shock unaccompanied by symptoms would also not be counted as the CASCADE primary end point of cardiac mortality. This set of definitions for patients with the automatic implanted cardioverter/defibrillator might decrease the number of actual primary end points counted, if one assumes that the device might activate and convert a potentially fatal arrhythmia before the patient develops syncope. Nevertheless, without a record of events available from a memory device built into the unit itself, it is impossible to document VF as the inciting event for the automatic implanted cardioverter/defibrillator shock, and we prefer to err on the side of undercounting events.

If a patient were to die from amiodarone pulmonary toxicity, it would be counted as a "cardiac" death in this study, because it would be a death directly related to the cardiac condition and its treatment.[23]

The null hypothesis of this study states that there is no difference in mortality between patients treated with amiodarone and patients treated with conventional agents. Overall mortality in this high-risk group is expected to be 40% at 2.5 years, 29% arrhythmic and 11% nonarrhythmic.[1–4] Our proposed alternative to the null hypothesis is that amiodarone decreases arrhythmic mortality from 29 to 10% and that it does not affect nonarrhythmic mortality. Assuming 124 patients in each group, the power to detect a decrease in arrhythmic mortality from 29 to 10% in the amiodarone group is 0.91. Data are analyzed with standard multivariate analysis, and life-table survival curves.

Our original intention was to analyze survival in the CASCADE study every 6 months. If the difference in survival between the amiodarone and conventional groups was markedly different ($p < 0.01$), the study would be terminated prematurely. At the third analysis on October 1, 1988, we instituted a revised monitoring plan, which used a more conservative stopping rule. Because enrollment was slightly behind schedule, and because the event rate was slightly lower than predicted, we decided to analyze the data only 3 more times between October 1, 1988, and March 31, 1991, the projected date of the end of patient enrollment. Analyses would occur at the 30th, 40th and 50th deaths among conventional patients. Therefore, the fourth analysis of survival would occur at the 30th death among patients treated with conventional agents, the fifth at the 40th, and the sixth at the 50th. The schedule assumed a 40%

TABLE II Baseline Characteristics of the 199 Patients

Characteristic	Total (%) (n = 199)	Amiodarone Therapy* (%) (n = 98)	Conventional Therapy* (%) (n = 101)
Male gender	176 (88)	89 (91)	87 (86)
Age (yr)	62 ± 10	62 ± 10	62 ± 11
Coronary artery disease	161 (81)	81 (83)	80 (79)
Prior myocardial infarction	130 (81)	69 (85)	61 (76)
Non-coronary artery disease	38 (19)	17 (17)	21 (21)
Congestive heart failure	89 (45)	47 (48)	42 (42)
Prior drug failure†	88 (44)	42 (43)	46 (46)
Prior cardiac surgery‡	112 (56)	56 (57)	56 (55)
Left ventricular ejection fraction	0.35 ± 0.15	0.35 ± 0.15	0.36 ± 0.14
VT or VF inducible at baseline electrophysiology study	70/155 (45)	33 (43)	37 (47)
Baseline Holter recording			
VPCs/hour	181 ± 247	149 ± 203	215 ± 282
Complex VPCs	150/168 (89)	76/85 (89)	74/83 (89)
VT	91/168 (54)	46/85 (54)	45/83 (54)
Drugs§			
Digitalis	70 (36)	32 (33)	38 (38)
Diuretics	89 (45)	41 (42)	48 (48)
Beta blockers	23 (12)	8 (8)	15 (15)
Nitrates	37 (19)	19 (20)	18 (18)
Antihypertensives	48 (24)	21 (22)	27 (27)
Calcium antagonists	38 (19)	20 (21)	18 (18)
Automatic implantable cardioverter/defibrillator	95 (48)	46 (47)	49 (49)

* All p >0.05, amiodarone versus conventional groups.
† Either (1) spontaneous sustained arrhythmias with adequate dose and serum level of drug, before or after index ventricular fibrillation event, or (2) inducible sustained arrhythmia with adequate dose and serum level of drug at electrophysiologic testing after index ventricular fibrillation event.
‡ Cardiac surgery either (1) before index ventricular fibrillation event or (2) between index ventricular fibrillation event and randomization.
§ In 2 patients, baseline data are incomplete (n = 197: 97 amiodarone, 100 conventional).
VF = ventricular fibrillation; VPC = ventricular premature complex; VT = ventricular tachycardia.

mortality, with a target enrollment of 124 patients in each group. Standard statistical methods[24–27] for 6 analyses and an overall 2-sided $p < 0.05$ indicate $p < 0.002$ as the stopping rule at analyses 4 and 5, and $p < 0.05$ for statistical significance at the sixth analysis. Because the 3 earlier analyses of the data had a more liberal stopping rule, we will have "spent" >0.01 but <0.03 of the 0.05 type I error by the last analysis. Thus, a test nominally significant at 0.05 at the last analysis will have actual significance somewhat >0.06. If the trial goes to full term, the actual significance level will be computed by a randomization test.

RESULTS

By October 1988, 142 patients had been randomized and, by May 1990, 199 patients had been randomized. An additional 33 patients were considered for this study because of clinical factors suggesting a high risk of recurrence of VF, but they had normal Holter recordings and electrophysiologic studies and were thus excluded from participation. The randomization process has successfully achieved equality in the amiodarone and the conventional groups with respect to all baseline characteristics (Table II). The clinical and demographic characteristics of patients in this series are similar to other series reported for survivors of out-of-hospital VF,[1–4] except that our current population has more prior drug failure and prior cardiac surgery. Electrophysiologic testing revealed inducible VT or VF in 70 of 155 (45%) of patients tested. In patients treated with conventional

TABLE III Drug Therapy at Discharge

Amiodarone n = 98

Conventional n = 101

Quinidine	31	Flecainide	11
Procainamide	23	Propafenone	1
Disopyramide	3	Combinations	12
Tocainide	4	Beta blocker only	1
Mexiletine	7	Crossed over to amiodarone	3
Encainide	0	None	5

TABLE IV Patient Enrollment

Randomization Group			Total	
CAD	EF ≤0.30	Drug Failure*	A	C
+	+	+	24	20
+	+	0	19	16
+	0	+	14	18
+	0	0	24	26
0	+	+	1	3
0	+	0	4	3
0	0	+	3	5
0	0	0	9	10
Total			98	101

* Either (1) spontaneous sustained arrhythmia with adequate dose and serum level of drug, before or after the index ventricular fibrillation event, or (2) inducible sustained arrhythmia with adequate dose and serum level of drug at electrophysiologic testing after index ventricular fibrillation event.
A = amiodarone; C = conventional therapy; CAD = coronary artery disease; EF = ejection fraction; + = present; 0 = absent.

drugs, 37 of 78 (47%) could be guided by the results of electrophysiologic testing. No patients were lost to follow-up, and only 8 patients in each group crossed over to the alternative therapy. Most conventionally treated patients received quinidine (Table III). Fifty-seven of the initial 142 patients (40%) also received the automatic implantable cardioverter/defibrillator. The implantation rate has increased from 11% in 1984 to 73% in 1990. Randomization groups are listed in Table IV.

The dose of amiodarone was progressively decreased throughout the course of follow-up (Figure 2), with adjustment based on adverse effects, changes in the 12-lead electrocardiogram, and Holter recordings. No patients were discharged while receiving any combination of amiodarone and conventional agents. Patients received relatively low doses of amiodarone (229 ± 128 mg/day after the initial 3 months of decreasing doses) in an attempt to avoid serious side effects. Pulmonary toxicity was nevertheless not rare: 7% at 1 year and 11% at 3 years. No patient died of pulmonary toxicity. Pulmonary toxicity resolved slowly after amiodarone was discontinued, and most patients were left with residual impairment of exercise tolerance or pulmonary diffusing capacity, or both. One patient stopped amiodarone because of mental status changes, probably unrelated to amiodarone. No other potentially serious neurotoxicity was identified with these doses of amiodarone.

The primary end point of the study, total cardiac mortality, was 19% at 1 year and 44% at 3 years (Figure 3) in the initial 142 patients analyzed in October 1988. These percentages do not include patients who experienced only recurrent sustained VT. Seventeen percent of the 142 patients at 1 year and 35% of patients at 3 years (Figure 4) had "fatal" sustained arrhythmic events (sudden arrhythmic death and resuscitated out-of-hospital VF).

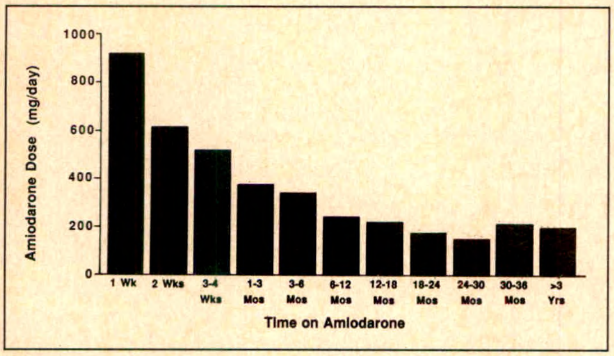

FIGURE 2. Average dose of amiodarone. Initially high doses were tapered to a mean maintenance dose of 170 ± 73 mg/day at 2 years.

DISCUSSION

This report outlines the protocol of a study comparing treatment of high-risk survivors of out-of-hospital VF with either (1) empiric amiodarone therapy or (2) other antiarrhythmic drug therapy guided, when possible, by electrophysiologic testing, the so-called "conventional" treatment. The enrollment goal for this study is 248 patients by March 31, 1991. All patients in this study have a high risk of recurrent VF, and no patient with a Q-wave myocardial infarction at the time of initial out-of-hospital VF is included. All patients are treated with antiarrhythmic drugs. The preliminary report of the Cardiac Arrhythmia Suppression Trial in 1989 raised questions about the usefulness of antiarrhythmic drug therapy, but tested a very different patient population.[28] It was considered unreasonable to treat high-risk VF survivors with a placebo when our study was designed in 1982. It is possible that drug therapy might worsen outcome in patients with a history of VF who have a high risk of recurrence, but the only way that a study could be performed ethically with a placebo would be to implant the automatic implantable cardioverter/defibrillator in all patients and treat half with a drug and half with a placebo. Such a device-based protocol was not feasible when the CASCADE study was begun, because the device itself was still experimental. Only such a study will reveal if a drug is better than a placebo. However, in order to perform such a study, it will be necessary to know which is an

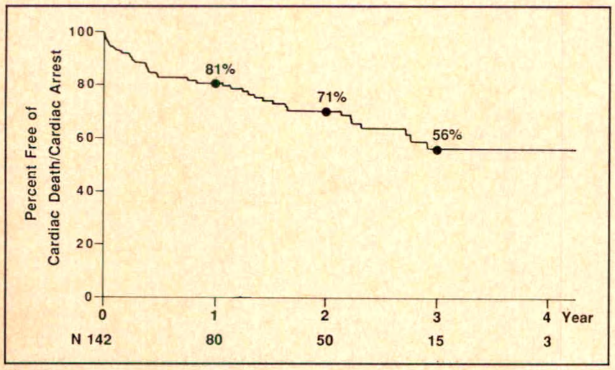

FIGURE 3. Total cardiac mortality in CASCADE. Percent survival is plotted versus time. The primary end point is any cardiac death or cardiac arrest, resuscitated or not. Recurrent sustained ventricular tachycardia is not counted as an end point in this analysis, even if it results in temporary loss of consciousness.

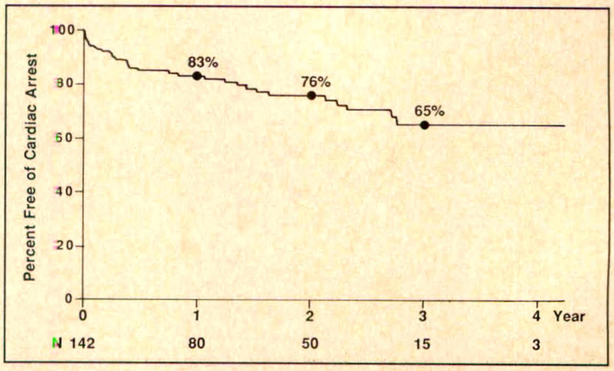

FIGURE 4. Recurrence of cardiac arrest, resuscitated or not, in CASCADE. Percent survival is plotted versus time. Patients are censored for noncardiac death and nonarrhythmic cardiac death. Recurrent sustained ventricular tachycardia is not counted as an end point in this analysis, even if it results in a temporary loss of consciousness.

effective antiarrhythmic strategy to compare against placebo. At the end of the CASCADE study, with knowledge of an effective approach to drug therapy, it may be possible to design such a study. By then, defibrillators with memory storage of cardiac rhythm may be available, making interpretation of shocks more accurate.

Low-dose amiodarone has proved to be a relatively safe treatment, with an acceptable incidence of serious pulmonary toxicity or neurotoxicity. Although it is possible that more patients could develop amiodarone-induced pulmonary toxicity as the study progresses, an incidence of 11% at 2 years seems tolerable in this high-risk patient population. To date, no patients have died of amiodarone-induced pulmonary toxicity.

This study highlights the difficulty in interpreting events in the presence of an automatic implanted cardioverter/defibrillator that does not store information about the rhythm shocked. It is quite possible that if the device functions before the time that a patient loses consciousness, events that would otherwise have been fatal would not be counted as end points in the CASCADE study. Nevertheless, we decided that loss of consciousness followed by an automatic defibrillator shock probably represents a serious arrhythmic event that should be counted in the total cardiac mortality category. At the final analysis of the CASCADE study, all automatic defibrillator shocks will also be separately analyzed with respect to the 2 drug treatment groups.

With the enrollment of nearly half of the patients anticipated in the study, it became obvious that total cardiac mortality and sudden arrhythmic cardiac mortality were much higher than reported for a series of patients with the implanted automatic defibrillator.[29] Although such series are not necessarily comparable with the Seattle population, we believed that an arrhythmic event rate of 17% at 1 year and 35% at 3 years with aggressively monitored drug therapy was too high, even though the drug therapy was chosen by what were thought to be the best possible indicators of successful drug therapy—namely, electrophysiologic testing and frequent Holter recording. In addition, patients were followed at close intervals, and drug therapy was monitored intensely at follow-up, with serum drug levels, Holter monitors and assessment of symptoms. Nevertheless, with such a high percentage of patients having VF at follow-up, we changed the protocol to include automatic defibrillator implantation in all patients in whom it was surgically feasible. Since that decision, 67% of patients have had the device implanted, compared with 40% before October 1988.

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APPENDIX

The CASCADE Investigators

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Relation of Cardiac Output at Rest and During Exercise to Age in Essential Hypertension

Robert Fagard, MD, PhD, and Jan Staessen, MD, PhD

It has been suggested that the decline of cardiac output with age is due to increased prevalence of disease, particularly occult coronary artery disease. Therefore, the relation of cardiac output (direct oxygen Fick method) to age was analyzed in 110 sixteen- to 64-year-old men with World Health Organization stage I or II essential hypertension at the time of the hemodynamic study, who were alive and free of cardiovascular complications 7 years later. At supine and seated rest, during upright bicycle exercise at 50 W and at peak work load, cardiac output was inversely (p <0.01) related to age. These relations were independent of weight and mean intraarterial pressure. Stroke volume decreased with advancing age at supine rest, but not at rest and during exercise in the seated position. Heart rate was not affected by age in the supine position, but was slower in older patients during upright rest and at peak exercise. In conclusion, in patients with essential hypertension who remained free of cardiovascular complications for 7 years, cardiac output was independently and inversely related to age at various levels of activity. These findings suggest that occult cardiovascular disease does not explain the decline in cardiac output with age in patients with essential hypertension.

(Am J Cardiol 1991;67:585–589)

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Cardiac output decreases with advancing age in patients with essential hypertension, at rest[1–6] and during exercise.[6,7] Similar observations have been reported in normotensive subjects.[2,4,8–15] However, in active community dwellers in whom occult coronary artery disease was virtually excluded, aging was not associated with a decline in cardiac output at rest[16,17] and during effort.[16] Because hypertension is a cardiovascular risk factor, the lower cardiac output in the older hypertensive patients could be due to latent complications of hypertension. To test this hypothesis, we analyzed hemodynamic data obtained at rest and during exercise in patients with essential hypertension, classified as World Health Organization stage I or II at the time of the investigation, who were alive and free of cardiovascular disease 7 years after the hemodynamic study. It is reasonable to assume that the observations on cardiac output were not influenced by occult cardiovascular complications or other diseases. Furthermore, the possible confounding effect of blood pressure, per se, on the age-related decline of cardiac output[7,17–21] was studied with multiple regression analysis.

METHODS

Study population: The present analysis includes male patients who were referred, mostly by family physicians, to the Hypertension Unit of the University Hospitals of Leuven between 1972 and 1982, and who underwent a hemodynamic study at rest and during exercise. The routine investigation included history, clinical examination, appropriate laboratory tests, eye-fundus examination, electrocardiography at rest (and at exercise in case of a history of angina pectoris), pulmonary function tests, intravenous urography and renal arteriography when indicated. Patients were excluded when a specific cause of hypertension could be detected, or when World Health Organization stage III organ damage was present at the time of the investigation. Patients with evidence of ischemic heart disease, heart failure, claudication, cerebrovascular accident or renal insufficiency were thus excluded. No patient had valvular heart disease. All patients were in sinus rhythm and none had evidence of pulmonary disease. Patients had never been treated for high blood pressure or had their antihypertensive medication stopped for ≥2 weeks.

After the baseline examination, patients were referred to their usual source of care. The vital status of the patients was determined in 1989 through contacts with municipal authorities. Causes of death were ascertained from contacts with physicians or family mem-

bers, or both, and from hospital files and autopsy reports if available. The health status of living patients was determined by extensive questionnaires filled out by physicians or, in case of nonrespondents, by shorter questionnaires filled out by patients; if necessary, patients were contacted by telephone. In addition, the charts of patients followed at the University Hospitals in Leuven were checked for possible events. When cardiovascular events had occurred, the responsible physicians were contacted and all available documents concerning the events were checked. Events were coded according to the Ninth Revision of the International Classification of Diseases. The following events were considered: death, myocardial infarction, cerebrovascular accident, heart failure, angina pectoris, transient ischemic attack and intermittent claudication.

The hemodynamic study was performed in 124 patients with essential hypertension. In the subsequent 7 years, 8 patients died and 6 had a nonfatal cardiovascular complication. The present analysis was restricted to the remaining 110 patients.

Hemodynamic study: All hemodynamic measurements were performed in the morning in the same laboratory, where room temperature was 18 to 22°C, a few days after hospital admission. Patients gave informed consent after the nature of the procedures had been explained. The brachial artery was cannulated to measure intraarterial pressure and to sample arterial blood. A venous catheter (Swan-Ganz, 93.110.5Fr) was introduced in the antecubital vein and positioned in the pulmonary artery to sample mixed venous blood. Pressures were registered on a Mingograph 81 recorder. Uptake of oxygen and carbon dioxide output were measured continuously by the open-circuit method (standard temperature pressure dry). Minute-volume (body temperature pressure saturated) was determined by a pneumotachograph, and oxygen and carbon dioxide concentrations by a paramagnetic and an infrared gas analyzer, respectively. Cardiac output (liters/min) was determined by the direct oxygen Fick method. Systemic vascular resistance was calculated from mean brachial artery pressure, obtained by electrical damping, and cardiac output. Heart rate (beats/min) was recorded from the electrocardiogram. Stroke volume (ml) was calculated from cardiac output and heart rate.

A first set of measurements was obtained during supine rest, 30 minutes after the technical procedures. The patients were then seated on an electromagnetically braked bicycle ergometer and the rest sitting measurements were obtained 10 minutes later. A graded uninterrupted exercise test was then started at a work load of 20 W for 4 minutes and the load was increased by 30 W every 4 minutes until exhaustion. Cardiac output was determined at supine and sitting rest, at every other step during exercise and at the final work load; during exercise, cardiac output was determined during the last minute.[22,23]

Statistical analysis: Data are reported as mean ± standard deviation. At supine and seated rest, at 50 W and at peak work load, the hemodynamic variables were related to age in single regression analysis. In a second step, multiple regression analysis was used to test whether the associations of cardiac output and stroke volume with age were independent of weight and mean brachial artery pressure.

RESULTS

Patient characteristics: The age of the 110 men averaged 33 years (range 16 to 64). They had never been treated for high blood pressure (40%), or antihypertensive treatment had been stopped for an average of 5 weeks (range 2 to 28). The percentage of patients who had been receiving diuretics was 63%; 63% were receiving β blockers; 36% were receiving centrally active drugs, and various other drugs had been used by 20% of the patients. Mean weight was 78.3 ± 11.7 kg with a mean height of 175 ± 7 cm. Blood pressure on admission averaged 169 ± 26/106 ± 20 mm Hg, and intraarterial pressure 30 minutes after supine rest averaged 153 ± 24/83 ± 16 mm Hg. At supine rest, cardiac output averaged 7.8 ± 1.8 liters/min, heart rate 77 ± 13 beats/min and stroke volume 104 ± 27 ml. Cardiac output decreased in the seated position to 6.3 ± 1.4 liters/min and increased with exercise, reaching 17.8 ± 4.1 liters/min at peak work load (169 ± 43 W). Peak heart rate averaged 176 ± 22 beats/min, oxygen uptake 2.4 ± 0.6 liters/min and the respiratory exchange ratio 1.06 ± 0.11.

Single regression analysis (Table I, Figure 1): AT REST: Cardiac output was inversely related to age in both the supine and sitting positions. Stroke volume in the supine position and heart rate in the seated position were negatively correlated with age. Oxygen uptake was inversely and arteriovenous oxygen content difference positively related to age in each position. Systemic vascular resistance increased with age.

AT SUBMAXIMAL EXERCISE: At the fixed work load of 50 W, cardiac output declined significantly with advancing age. Heart rate and stroke volume tended to decrease, but these relations were not statistically significant. Older age was associated with a decreased oxygen consumption and a higher arteriovenous oxygen content difference. Systemic vascular resistance was lower during exercise than at rest, but remained positively associated with age.

AT PEAK EXERCISE: The inverse correlations of cardiac output, heart rate and oxygen uptake with age were highly significant. Peak stroke volume, however, was not affected by age. Older age was associated with a significantly higher systemic vascular resistance. Peak work load (W) decreased with advancing age (219 − 1.5 × age; $r = -0.41$; $p < 0.001$). The peak respiratory exchange ratio was not related to age ($r = -0.10$; $p = 0.29$). Mean pulmonary artery and capillary wedge pressures could be measured at peak exercise in 102 and 84 patients, respectively, and were not significantly related to age ($r = 0.03$, $p = 0.78$, and $r = 0.02$, $p = 0.86$).

Multiple regression analysis: Adjustment for weight and mean brachial artery pressure did not materially alter the regression coefficients of the relations of cardiac output and stroke volume to age. At supine and seat-

TABLE I Intercept, Regression Coefficient (Slope) and Correlation Coefficient of the Relations Between Various Hemodynamic Variables and Age at Supine and Sitting Rest, at 50 W and at Peak Exercise

	Rest						Exercise					
	Supine			Sitting			50 W			Peak		
	a	b	r	a	b	r	a	b	r	a	b	r
Cardiac output (liters/min)	10.1	−0.070	−0.45†	7.64	−0.042	−0.36‡	13.8	−0.062	−0.29†	21.4	−0.110	−0.32‡
Heart rate (beats/min)	81	−0.14	−0.13	98	−0.35	−0.26†	114	−0.24	−0.16	203	−0.82	−0.44‡
Stroke volume (ml)	128	−0.72	−0.32‡	80.8	−0.18	−0.11	123	−0.33	−0.15	107	−0.13	−0.06
Oxygen uptake (ml/min)	367	−1.65	−0.35‡	408	−1.52	−0.29†	1,065	−2.48	−0.25†	3,030	−19.8	−0.41‡
(A–V)O_2 diff. (ml/liter)	35.4	+0.18	+0.30†	52.7	+0.20	+0.25†	76.7	+0.29	+0.25†	144	−0.29	−0.16
MBAP (mm Hg)	99	+0.29	+0.18	103	+0.34	+0.21*	112	+0.40	+0.23*	119	+0.48	+0.23*
SVR (mm Hg/liter/min)	8.9	+0.18	+0.41‡	12.3	+0.21	+0.44‡	7.56	+0.11	0.42‡	5.16	+0.087	+0.40‡

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.
a = intercept; b = slope; (A–V)O_2 diff. = arteriovenous oxygen content difference; MBAP = mean brachial artery pressure; r = correlation coefficient; SVR = systemic vascular resistance.

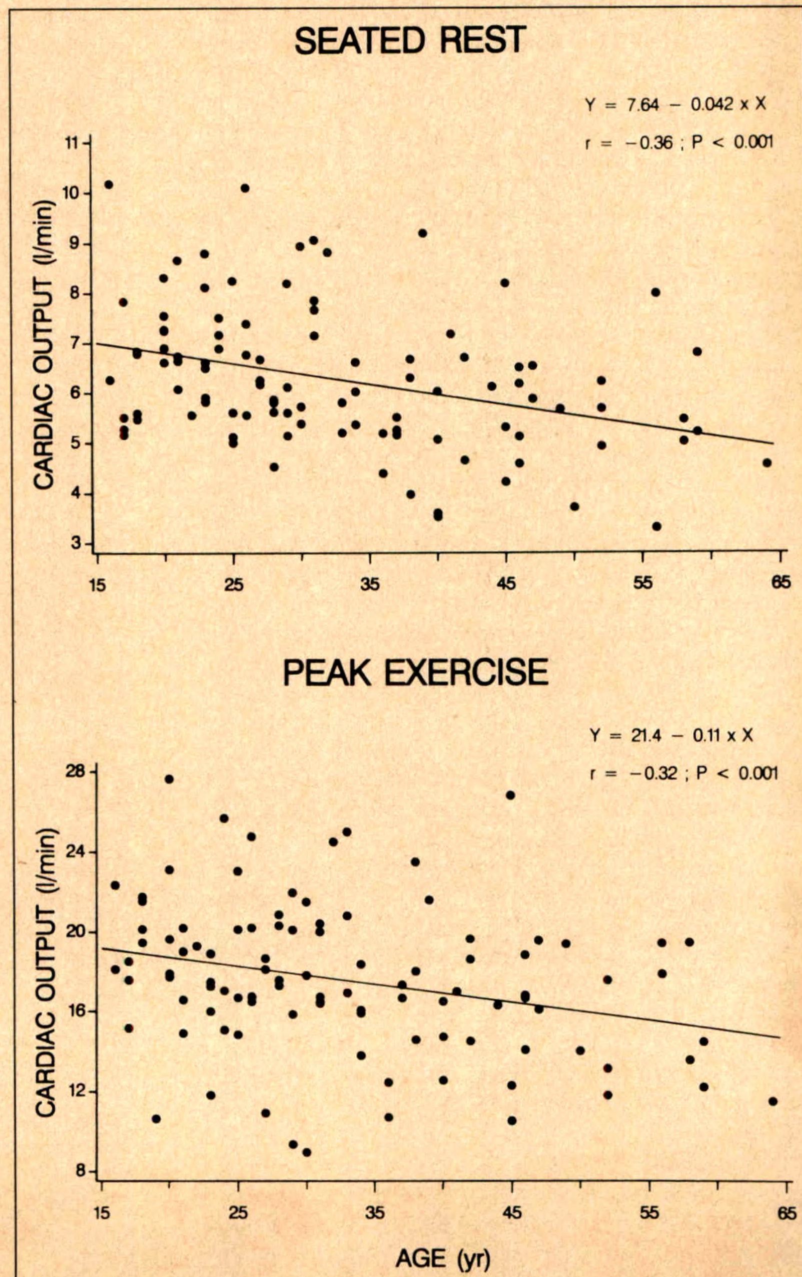

FIGURE 1. Relation between cardiac output (liters/min) and age (years) at rest in the seated position *(upper panel)* and at peak exercise *(lower panel).*

ed rest, at 50 W and at peak work load, these regression coefficients were, respectively, −67, −45, −68 and −118 ml/min ($p < 0.001$ for all) for cardiac output, and −0.62 ($p < 0.01$), −0.16 (difference not significant), −0.26 (difference not significant) and −0.10 ml (difference not significant) for stroke volume.

DISCUSSION

The results of the cross-sectional post-hoc analysis of the Baltimore Longitudinal Study on Aging[16] caused much debate because, unlike most other previous studies of normal subjects,[2,4,8-15] cardiac output at rest and during exercise did not decrease with advancing age. Differences with previous studies were the noninvasive techniques used to assess cardiac output and the selection of the subjects. They had to be physically active and free from cardiovascular disease, as evidenced by a normal electrocardiogram, myocardial scintigram and ventriculogram during exercise. These results were confirmed for cardiac output at rest, using the invasive dye dilution method in a population with similar characteristics.[16] The majority of studies in normal humans, however, reported a decrease of cardiac output with advancing age, both at rest and during exercise.

In patients with hypertension, cardiac output was found to decrease with advancing age.[1-7] Because hypertension is a risk factor, hemodynamic studies in hypertensive patients could be confounded by undetected cardiovascular lesions. In the present study, we hypothesized that it is unlikely that subclinical disease influenced the hemodynamic data, because only patients classified as World Health Organization stage I or II at the initial investigation and who were alive and free of cardiovascular complications 7 years later were included in the analysis. Cardiac output was inversely related to age at rest, at submaximal exercise and at peak exercise, and these relations were independent of weight and of mean brachial artery pressure.

Cardiac output can be analyzed as the product of heart rate and stroke volume or as the ratio of oxygen uptake on the arteriovenous oxygen difference. At supine rest the decline of cardiac output with age was based on a decrease in stroke volume, whereas in the seated position, heart rate was significantly reduced in older patients. Oxygen uptake at rest decreased with age, suggesting that part of the lower cardiac output can be explained by the lower metabolic needs of the aging body. However, the wider arteriovenous oxygen difference at higher ages indicates that the flow of blood to the tissues is inadequately low and that the oxygen demand of the periphery is satisfied by an increased peripheral oxygen extraction. The observations on the age relations of cardiac output, oxygen uptake and the arteriovenous oxygen difference at the fixed submaximal work load of 50 W were similar to the data at rest.

Peak cardiac output was significantly lower in older patients. Because the arteriovenous oxygen difference at peak exercise was not related to age, the reduced cardiac output can be ascribed to the lower peak oxygen uptake and exercise capacity. As in many other studies, peak heart rate declined with age. Despite the lower work load achieved, older subjects reached the same peak stroke volume as younger ones, but stroke volume did not increase to an extent that it could overcome the lower heart rate. The pulmonary wedge pressure at peak exercise was not altered by age. This, together with the observation that the decrease of cardiac output with age was related to heart rate and not to stroke volume, suggests that the decrease in peak cardiac output with age cannot be explained by impaired left ventricular function.

Study limitations: Data were collected in hypertensive patients <65 years, so that no inference can be drawn for normal subjects and older patients. Although it is likely that the selected patients were free of occult cardiovascular disease at the time of the hemodynamic study, there is no definite proof for this assertion. None of the patients trained extensively, but differences in habitual physical activity, which was not assessed in detail, could have contributed to the differences between younger and older patients.

Acknowledgment: We gratefully acknowledge the secretarial assistance of Nicole Ausseloos and the technical assistance of Jos Delsupehe, Tine Mussen and Julien Romont.

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Comparison of the Effects of Guanadrel Sulfate and Propranolol on Blood Pressure, Functional Capacity, Serum Lipoproteins and Glucose in Systemic Hypertension

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In a controlled, double-blind, crossover study, the effects of guanadrel sulfate and propranolol on blood pressure (BP) and selected cardiopulmonary and metabolic variables were compared in 15 physically active and moderately hypertensive subjects. Guanadrel sulfate reduced systolic and diastolic BP at rest by −16 and −15 mm Hg, and at maximal exercise by −33 and −13 mm Hg, respectively ($p < 0.005$), without affecting submaximal oxygen consumption ($\dot{V}O_2$), maximal $\dot{V}O_2$, ventilatory threshold, forced vital capacity, forced expiratory volume in 1 second, or fatigue, as assessed by perceived exertion. In contrast, propranolol significantly decreased diastolic BP at rest (−16 mm Hg) and systolic BP at maximal exercise (−44 mm Hg); however, it significantly decreased submaximal $\dot{V}O_2$ (−3.9 $ml \cdot kg^{-1} \cdot min^{-1}$), maximal $\dot{V}O_2$ (−3.9 $ml \cdot kg^{-1} \cdot min^{-1}$), ventilatory threshold (−0.3 $liters \cdot min^{-1}$), minute ventilation at submaximal exercise (−7.3 $liters \cdot min^{-1}$), forced expiratory volume in 1 second (−0.27 liters), and concomitantly increased the rating of perceived exertion at maximal exercise (1.9 U). Guanadrel sulfate was also associated with significant decreases in mean fasting plasma glucose and total serum cholesterol, whereas propranolol resulted in an increase in serum triglycerides ($p < 0.05$). In contrast to propranolol, guanadrel sulfate appears to decrease BP without evoking negative metabolic consequences or impairing exercise tolerance.

(Am J Cardiol 1991;67:590–596)

Increasing numbers of medically treated patients with hypertension are being encouraged to participate in regular aerobic exercise.[1–3] However, certain antihypertensive agents, notably β blockers, have been shown to decrease aerobic capacity,[4–11] impair physical training benefits,[4,7,9,11,12] reduce exercise duration,[4,13–15] and increase the rating of perceived exertion at submaximal[13] and maximal exercise levels,[5] effects that might be mediated by the metabolic actions of these drugs on intracellular potassium flux,[13,14] energy substrate availability,[9,14–16] or both. Additionally, β blockers can adversely affect serum lipids and carbohydrate metabolism.[17]

We compared the relative antihypertensive efficacy of the nonselective β blocker, propranolol, with that of guanadrel sulfate, and examined the effects of these drugs on selected cardiorespiratory, metabolic and lipid variables before, during and after maximal exercise testing. Whereas propranolol lowers blood pressure (BP), in part by decreasing cardiac output, guanadrel sulfate inhibits the release of norepinephrine from presynaptic storage sites and depletes this neurotransmitter from nerve endings, resulting in relaxation of vascular smooth muscle.

METHODS

Subjects: Fifteen physically active subjects (13 men, 2 women) with essential hypertension, who had been exercising regularly (≥30 min/day, 3 times/week), were recruited by radio and newspaper advertisements. After obtaining informed consent, a medical history, physical examination, resting electrocardiogram and routine laboratory tests were obtained, and subjects were instructed not to change their diet or exercise habits during the 4-month duration of the study. Twelve subjects who were receiving drug therapy were weaned from their antihypertensive medication over a 2-week period. To qualify for the study, the mean of 3 sitting diastolic BPs, measured when subjects were not taking antihypertensive medication, had to fall between 95 and 110 mm Hg.

Protocol: A randomized, double-blind, 2-way crossover design was used. For the first 4 weeks of the study, subjects took a placebo tablet every 12 hours. They met weekly with a nurse for measurements of BP, heart rate and body weight, and reported adverse events from the preceding week. At the end of the 4-week placebo-baseline period, subjects underwent a maximal graded

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treadmill exercise test, and were then randomly assigned to ≥4 weeks of drug therapy with either guanadrel sulfate or propranolol. Guanadrel sulfate was titrated weekly by increments of 10 mg/day, from 5 mg twice a day to a maximum of 20 mg twice a day, whereas propranolol was titrated weekly by increments of 80 mg/day, from 40 mg to a maximum of 160 mg twice a day, or until a significant BP reduction—defined as a sitting diastolic pressure of <90 mm Hg or a decrease in diastolic pressure ≥10 mm Hg from baseline—was observed. If this response was not achieved after 4 weeks, drug therapy was extended for another week, with guanadrel sulfate increased to 30 mg twice a day and propranolol increased to 240 mg twice a day.

On completion of the first 4-week drug therapy period, subjects underwent a second exercise test and then began a 4-week washout period. Those given guanadrel sulfate received a placebo for 4 weeks, whereas those given propranolol were tapered off of the medication for 2 weeks and then given a placebo for 2 more weeks. At the end of this placebo washout phase, subjects underwent a third exercise test, after which they were crossed over to the alternate drug for 4 or 5 weeks. The fourth exercise test was completed at the end of the second drug therapy phase.

Procedures: Two hours before each exercise test, and immediately before patients received their regular dose of medication, heart rate and BP measurements were obtained at rest, and a fasting blood sample was drawn to determine the levels of potassium, glucose, free fatty acids, norepinephrine, epinephrine, lactate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol. Plasma norepinephrine and epinephrine were analyzed by high-performance liquid chromotography. Plasma free fatty acids were determined by colorimetric analysis. Plasma glucose was measured by the ultraviolet method with hexokinase (Abbott VP). Serum potassium was assessed with analyzers fitted with ion-selective electrodes (Nova 4+4), and serum lactate was determined by a modification of the Marbach-Weil method[18] with a DuPont Automatic Clinical Analyzer. Total serum cholesterol was measured directly by the enzymatic method with cholesterol esterase and oxidase; high-density lipoprotein cholesterol was similarly assayed after magnesium dextran sulfate precipitation of lower density lipoproteins. Triglycerides were measured with glycerol phosphate oxidase. Blood samples were also obtained immediately and 30 minutes after exercise to remeasure these variables.

Maximal cardiorespiratory performance was assessed with the continuous multistage treadmill protocol of Bruce et al.[19] The first stage of the protocol (1.7 miles/hour^{-1}, 10% grade) was defined as the standard submaximal work load. Respiratory variables, heart rate, BP (auscultatory method), rate-pressure product, and somatic fatigue, assessed by the rating of perceived exertion, were determined at submaximal and maximal exercise. Expired gas was collected and analyzed continuously. The electrocardiograph was monitored by oscilloscope, with 3-channel (V_1, V_5 and aVF) recordings obtained throughout the exercise test and 12-lead electrocardiograms recorded at the end of each stage and during maximal exercise. The rate-pressure product was calculated as: [(heart rate × systolic BP)/100]. Ratings of perceived exertion were obtained with the Borg scale,[20] which includes 15 grades from 6 to 20: 7 = very, very light, 9 = very light, 11 = fairly light, 13 = somewhat hard, 15 = hard, 17 = very hard, and 19 = very, very hard.

Cardiopulmonary data were obtained by the Medical Graphics CAD/Net System 2001. The gas analysis system included a 2-way (inspired-expired) low deadspace breathing valve; oxygen and carbon dioxide analyzers using the electrochemical cell (yttria-stabilized zirconium dioxide) and infrared absorption principles, respectively; pneumotachographic volume measurement; and a computer assembly for on-line 60-second calculations, corrected to body temperature, atmospheric pressure saturated, or standard temperature and pressure, dry, of oxygen uptake ($\dot{V}O_2$), expressed in liters per minute (liters·min^{-1}) or METs (1 MET = 3.5 ml·kg^{-1}·min^{-1}), minute ventilation, carbon dioxide production ($\dot{V}CO_2$), and respiratory exchange ratio ($\dot{V}CO_2$/ $\dot{V}O_2$). Before each test, the pneumotachometer was referenced with a 3-liter syringe (Hans Rudolph, Inc.) and the gas analyzers were calibrated using room air and a certified O_2/CO_2 concentration (Airco Medical Gases, Inc.).

The anaerobic or ventilatory threshold was defined as the point of increase in minute ventilation/$\dot{V}O_2$ during graded exercise, without a change in minute ventilation/$\dot{V}CO_2$ (Figure 1). This method has been reported to be a sensitive and reliable noninvasive technique for detection of the onset of metabolic acidosis.[21] In addition, functional aerobic impairment—defined as the percent difference between the subject's measured maximal $\dot{V}O_2$ and that predicted for a healthy person of the same age, sex, and activity status—was calculated from the following formula: (predicted maximal $\dot{V}O_2$ − measured maximal $\dot{V}O_2$/ predicted maximal $\dot{V}O_2$) × 100. Predicted values of maximal $\dot{V}O_2$, expressed as

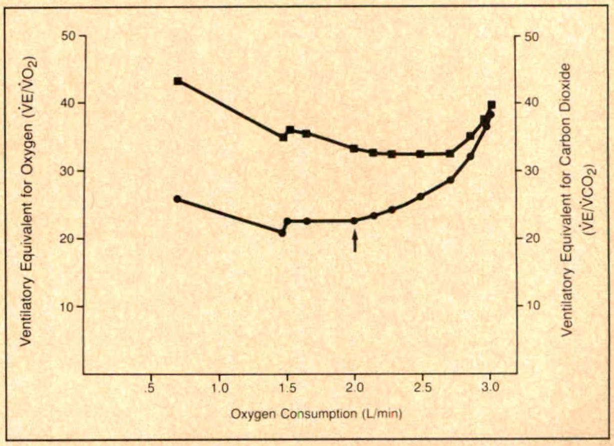

FIGURE 1. Ventilatory equivalent for oxygen *(closed circles)* and carbon dioxide *(closed squares)* as a function of oxygen consumption for 1 subject. *Arrow* indicates ventilatory threshold, which occurred at 67% of the maximal oxygen consumption.

TABLE I Baseline Characteristics of 15 Moderately Hypertensive Patients

	Mean	SD
Age (years)	48	9
Height (cm)	176	8
Weight (kg)	85	19
Body mass index (kg/m^2)	27	4
Resting systolic BP (mm Hg)	160	22
Resting diastolic BP (mm Hg)	108	5
Maximal systolic BP (mm Hg)	231	13
Maximal diastolic BP (mm Hg)	101	10
Maximal heart rate (beats·min^{-1})	174	15
Maximal rate pressure product	400	29
Maximal $\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	30	8
Maximal rating of perceived exertion	16	2
Treadmill duration (min)	10.5	2
Functional aerobic impairment (%)	10.8	22.8
Maximal minute ventilation (liters·min^{-1})	97	28
Ventilatory threshold (liters·min^{-1})	1.8	0.5
Forced vital capacity (liters)	4.2	0.7
Forced expiratory volume (liters·s^{-1})	3.5	0.8
Total cholesterol (mg/dl)	214	31
HDL cholesterol (mg/dl)	55	15
LDL cholesterol (mg/dl)	124	20
Total/HDL cholesterol	3.9	1
Triglycerides (mg/dl)	240	215

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; $\dot{V}O_2$ = oxygen consumption.

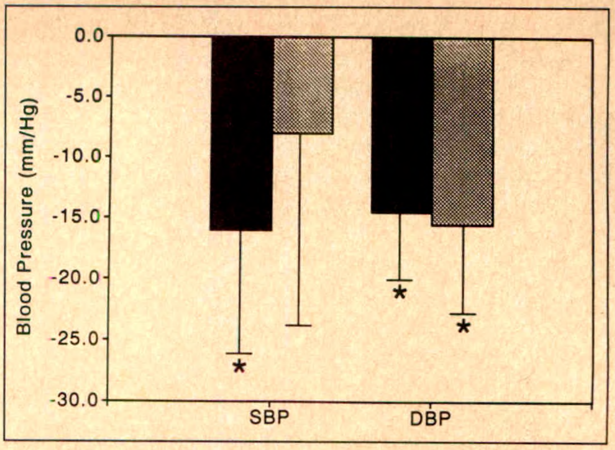

FIGURE 2. Mean reductions in systolic (SBP) and diastolic (DBP) blood pressure at rest from placebo-baseline with guanadrel sulfate versus propranolol. *Solid bar* is guanadrel sulfate and *hatched bar* is propranolol. *Lines extending from bars* represent 1 standard deviation. *p <0.001.

ml·kg^{-1}·min^{-1}, in healthy men and women were obtained from the regression equations of Bruce et al.[19]

Electrocardiographic and heart rate determinations were made with the Marquette Computer-Assisted System for exercise. The electrocardiograph was calibrated to 1 mV/10 mm deflection before each test.

Patients exercised to exhaustion or volitional fatigue, or both, and assumed a supine position in recovery to facilitate the drawing of a blood sample immediately after exercise. Forced vital capacity and forced expiratory volume in 1 second were determined 6 minutes after exercise with a Collins Eagle 1 spirometer. The third blood sample was drawn 30 minutes after exercise.

Statistical methods: Data analyses included calculations of means and standard deviations with the statistical software package MIDAS.[22] To determine the effects of guanadrel sulfate and propranolol on BP at rest and on cardiopulmonary and metabolic variables, values obtained during exercise testing at the end of 4 weeks of either drug therapy were compared, by paired *t* test, with the corresponding values at the end of 4 weeks of placebo. Changes in these variables from placebo-baseline were also compared with each other by paired *t* tests (because of the crossover design). Pulmonary function data obtained 6 minutes after exercise with each drug were compared with corresponding data obtained

TABLE II Physiologic Changes from Baseline in Subjects Undergoing Treadmill Exercise Testing: Guanadrel Sulfate Versus Propranolol*

	Guanadrel Sulfate			Propranolol	
Variable	Mean	SD		Mean	SD
Maximal systolic BP (mm Hg)	−33†	22		−44†	18
Maximal diastolic BP (mm Hg)	−13†	8		−7	14
Duration on treadmill (min)	+0.6†	1		−0.4	1.2
Submaximal heart rate (beats·min^{-1})	−20†	8	§	−30†	8
Maximal heart rate (beats·min^{-1})	−21†	17	§	−53†	13
Submaximal rate pressure product	−63†	34		−85†	33
Maximal rate pressure product	−96†	61	‖	−161†	47
Submaximal $\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	−0.9	2.2	‖	−3.9‡	4.6
Maximal $\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	−0.8	3.5		−3.9‡	4.2
Submaximal rating of perceived exertion	−0.2	2.7		−0.5	1.7
Maximal rating of perceived exertion	+0.2	1.4	‖	+1.9†	1.7
Functional aerobic impairment (%)	+1	10		+12†	12
Ventilatory threshold (liters·min^{-1})	−0	0.3		−0.3‡	0.4
Submaximal minute ventilation (liters·min^{-1})	−1‡	4.3	§	−7.3†	7.3
Maximal minute ventilation (liters·min^{-1})	+3.1	14.2		−1.4	17.6

* One subject did not complete the fourth exercise test (n = 14).
† Difference from baseline is significant at p <0.005.
‡ Difference from baseline is significant at p <0.05.
§ Difference in changes from baseline between medications is significant at p <0.005.
‖ Difference in changes from baseline between medications is significant at p <0.05.
Submaximal = at standard submaximal work load, 1.7 miles/hour^{-1}, 10% grade.
Abbreviations as in Table I.

after exercise at placebo-baseline. Adverse events were compared with chi-square. All tests were 2-tailed and a p value <0.05 was considered statistically significant.

RESULTS

Table I provides mean (± standard deviation) physical, cardiopulmonary, hemodynamic, lipid and lipoprotein characteristics of the 15 subjects after 4 weeks of placebo. With the exception of the BP at rest (160/108 mm Hg), these values, for the most part, were normal.

Figure 2 compares the effects of guanadrel sulfate versus propranolol on mean systolic and diastolic BP at rest. Compared with values obtained during the placebo-baseline phase, both drugs significantly decreased diastolic BP at rest (15 vs 16 mm Hg, guanadrel sulfate vs propranolol, $p < 0.001$). Although the decrease of 16 mm Hg in systolic BP at rest was significant with guanadrel sulfate ($p < 0.001$), the decrease of 8 mm Hg in systolic BP with propranolol was not ($p > 0.05$). There was, however, no significant difference between these 2 drugs in their antihypertensive efficacy.

Mean changes in exercise variables: Table II compares the physiologic changes from placebo-baseline with guanadrel sulfate versus propranolol for exercise variables. There was a significant reduction in systolic BP at maximal exercise with both drugs (−33 vs −44 mm Hg, guanadrel sulfate vs propranolol, $p < 0.005$). There was also a statistically significant decrease in diastolic BP at maximal exercise with guanadrel sulfate (−13 mm Hg), but the decrease in diastolic BP with propranolol (−7 mm Hg) was not significant ($p > 0.05$). However, there were no statistically significant differences in the BP decreases between drugs. Treadmill duration increased slightly with guanadrel sulfate (+0.6 min, $p < 0.05$), but not with propranolol. Values for heart rate and rate-pressure product at submaximal and maximal exercise were significantly lower ($p < 0.005$) with both drugs, compared with placebo. However, the propranolol-induced decreases in heart rate at both exercise levels, and rate-pressure product at maximal exercise, were significantly greater than those elicited by guanadrel sulfate ($p < 0.05$).

Compared with placebo-baseline, subjects demonstrated statistically significant ($p < 0.05$) decreases in submaximal $\dot{V}O_2$ (-3.9 ml·kg^{-1}·min^{-1}) and maximal $\dot{V}O_2$ (-3.9 ml·kg^{-1}·min^{-1}) while taking propranolol, whereas the smaller decreases associated with guanadrel sulfate were not statistically significant ($p > 0.05$). The propranolol-induced reduction in submaximal $\dot{V}O_2$ was significantly greater than that with guanadrel sulfate (-3.9 vs -0.9 ml·kg^{-1}·min^{-1}, $p < 0.05$). Moreover, propranolol resulted in a statistically significant increase in perceived exertion at maximal exercise (+1.9, $p < 0.005$), which was significantly greater than the increase with guanadrel sulfate (+0.2, $p < 0.05$). Subjects taking propranolol also demonstrated a functional aerobic impairment of +12% ($p < 0.005$) and a decrease in their ventilatory threshold (-0.3 liters·min^{-1}, $p < 0.05$); in contrast, these variables were unchanged with guanadrel sulfate. Minute ventilation at submaximal exercise decreased significantly ($p < 0.05$) with both drugs, compared with placebo-baseline; however, the mean decrease with propranolol (-7.3 liters·min^{-1}) exceeded that with guanadrel sulfate (-1.0 liters·min^{-1}, $p < 0.005$).

As shown in Figures 3 and 4, when subjects took propranolol, forced vital capacity and forced expiratory volume in 1 second were reduced significantly (−0.30 and −0.27 liters, respectively; $p < 0.01$). There were no statistically significant changes with guanadrel sulfate ($p > 0.05$).

Mean changes in metabolic and hormonal variables: Table III compares changes from placebo-baseline for selected blood chemistry values associated with each drug. With guanadrel sulfate, plasma glucose levels before and immediately after exercise significantly decreased from placebo-baseline values (−11 mg/dl for both). Guanadrel sulfate also altered levels of epinephrine and norepinephrine immediately and 30 minutes after exercise. When subjects received propranolol, mean serum potassium levels increased at all time points (+0.23, +0.42, +0.46 mEq/liter, $p < 0.05$).

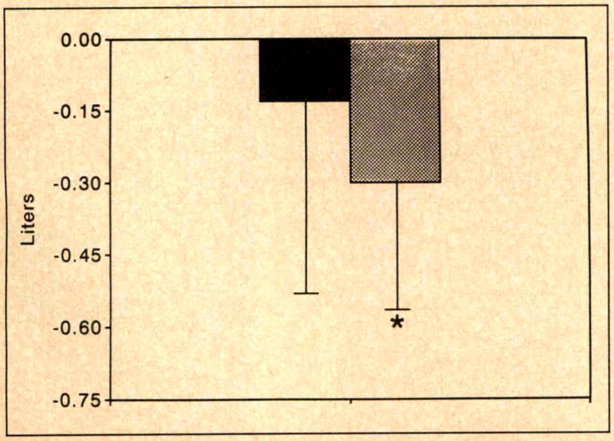

FIGURE 3. Mean decreases in forced vital capacity from placebo-baseline with guanadrel sulfate versus propranolol. *Solid bar* is guanadrel sulfate and *hatched bar* is propranolol. *Lines extending from bars* represent 1 standard deviation. *p <0.01.

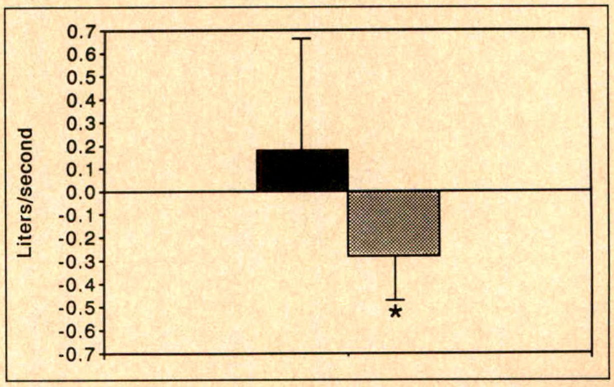

FIGURE 4. Changes in forced expiratory volume in 1 second from placebo-baseline with guanadrel sulfate versus propranolol. *Solid bar* is guanadrel sulfate and *hatched bar* is propranolol. *Lines extending from bars* represent 1 standard deviation. *p <0.001.

TABLE III Electrolyte, Substrate and Hormonal Changes from Baseline in Subjects Undergoing Treadmill Exercise Testing: Guanadrel Sulfate Versus Propranolol

	Guanadrel Sulfate		Propranolol	
Variable	Mean	SD	Mean	SD
Potassium (mEq/liter)				
Before	+0.10	0.40	+0.23†	0.24
Immediately	+0.01	0.65	+0.42*	0.59
30 min after	+0.05	0.30	+0.46†	0.36
Fasting glucose (mg/dl)				
Before	−11*	14	+2	11
Immediately	−11†	14.0	‡ +2	15
30 min after	−8	18	+1	13
Free fatty acids (mEq/liter)				
Before	+0.03	0.30	−0.04	0.19
Immediately	0	0	+0.12*	0.16
30 min after	−0.01	0.21	§ −0.21†	0.22
Epinephrine (pg/ml)				
Before	−12	33	+20	52
Immediately	+48*	68	§ +218†	240
30 min after	−2	52	+27	94
Norepinephrine (pg/ml)				
Before	−117	175	−19	249
Immediately	−864	1,812	+431	508
30 min after	−390*	509	−483	1,374
Lactate (mEq/liter)				
Before	−0.15	0.58	+0.13	0.57
Immediately	−0.48	1.43	−1.06	2.71
30 min after	−0.06	1.10	−0.63	1.47

* Difference from baseline is significant at p <0.05.
† Difference from baseline is significant at p <0.01.
‡ Difference in changes from baseline between medications is significant at p <0.05.
§ Difference in changes from baseline between medications is significant at p <0.01.
Before = before exercise; immediately = immediately after exercise; 30 min after = 30 minutes after exercise.
Other abbreviations as in Table I.

Moreover, free fatty acid levels for both postexercise samplings decreased (−0.12 and −0.21, $p < 0.05$), whereas epinephrine levels immediately after exercise increased (+218 pg/ml); this increase was statistically significantly greater than the increase with guanadrel sulfate (+48 pg/ml, $p < 0.01$).

Mean changes in lipids: Total cholesterol (Table IV) significantly decreased (−16 mg/dl, $p < 0.05$) from placebo-baseline when subjects received guanadrel sulfate; moreover, this effect differed significantly from the slight increase in cholesterol that occurred with propranolol ($p < 0.05$). Serum triglyceride levels were not affected significantly by guanadrel sulfate, but increased (+85 mg/dl, $p < 0.05$) with propranolol.

Adverse events: Adverse events reported by subjects are listed in Table V, with fatigue reported most often. Compared with 10 reports of fatigue while subjects received placebo, there were 6 instances with guanadrel sulfate (difference not significant) and 19 with propranolol ($p < 0.02$). No other adverse event was significantly affected by either drug.

DISCUSSION

In this double-blind study we found that guanadrel sulfate decreased systolic and diastolic BP at rest and decreased systolic and diastolic BP at maximal exercise ($p < 0.005$), without adversely affecting submaximal or maximal VO_2, perceived exertion or ventilatory thresh-

TABLE IV Lipid and Lipoprotein Changes from Baseline: Guanadrel Sulfate Versus Propranolol

	Guanadrel Sulfate		Propranolol	
Variable	Mean	SD	Mean	SD
Total cholesterol (mg/dl)	−16*	22	† +10	20
HDL cholesterol (mg/dl)	−1	9	−3	9
LDL cholesterol (mg/dl)	−6	21	4	31
Total/HDL cholesterol	−0.2	0.6	−0.2	1.2
Triglycerides (mg/dl)	−62	146	+85*	139

* Difference from baseline is significant at p <0.05.
† Difference in changes from baseline between medications is significant at p <0.05.
Abbreviations as in Table I.

TABLE V Comparison of Adverse Events While Subjects Received Placebo Versus Guanadrel Sulfate or Propranolol

Adverse Event	Placebo	Guanadrel Sulfate	Propranolol
Fatigue	10	6	† 19*
Lack of concentration	2	0	2
Vertigo	0	0	1
Pain	0	1	1
Retrograde ejaculation	1	2	0
Edema	10	0	3
Dry mouth	0	2	0
Headache	2	0	2

* Difference from baseline is significant at p <0.02.
† Difference in changes from baseline between medications is significant at p <0.02.

old. Total serum cholesterol levels, relative to placebo-baseline, were also favorably modified by this drug. Although propranolol reduced diastolic BP at rest and systolic BP at maximal exercise ($p < 0.005$), systolic BP at rest and diastolic BP at maximal exercise did not change significantly. Moreover, propranolol significantly decreased submaximal and maximal $\dot{V}O_2$ and ventilatory threshold, and increased the maximal rating of perceived exertion and serum triglyceride levels ($p < 0.05$). These findings, however, should be interpreted with caution. In several instances, differences between drugs were not statistically significant. Although this most likely reflects a type II error (resulting from the relatively small number of subjects studied), it is equally possible that some of the significant findings may reflect a type I error (resulting from the use of multiple *t* tests).

The propranolol-induced decrease in $\dot{V}O_2$ at submaximal and maximal exercise, a finding consistent with previous studies in trained[8,23] and untrained subjects,[8] may be attributed to a reduced cardiac output. Numerous studies have also shown that β blockade reduced exercise duration at submaximal and maximal work loads.[4,13,14] Despite unchanged treadmill duration and reduced maximal $\dot{V}O_2$ with propranolol, our subjects reported a higher perceived exertion at maximal exercise, indicating greater fatigue at a lower somatic oxygen consumption. This observation has been reported by others.[13] Some investigators hypothesized that the increased fatigue and reduced exercise duration could result from an enhanced cellular efflux of potassium that is mediated by β blockers.[13,14] When the present subjects were taking propranolol, a significant increase in serum potassium concentrations before and after exercise was noted, supporting this hypothesis; in contrast, potassium levels with guanadrel sulfate were unchanged.

The anaerobic or ventilatory threshold has become a valuable measurement in the assessment of cardiorespiratory function. Although controversial, it is thought to signify the peak work load, or metabolic rate, at which oxygen demands exceed the circulation's ability to sustain aerobic metabolism.[24] At this point, energy release from anaerobic metabolism increases and a lactic acidemia results. In the present study, ventilatory threshold remained unchanged with guanadrel sulfate, but significantly decreased ($p < 0.05$) with propranolol (Table II), as others have found.[10,25] This finding may help to explain the previously reported reduction in exercise duration at submaximal work loads in subjects taking propranolol,[7,14] perhaps because the utilization of carbohydrate is impaired by this nonselective β blocker,[26] causing greater reliance on free fatty acids for energy usage. Reduced free fatty acid levels after exercise with propranolol but not with guanadrel sulfate (Table III) may support this hypothesis.[15]

Decreases in forced vital capacity and forced expiratory volume in 1 second with propranolol (−0.3 and −0.27 liters, respectively; $p < 0.01$) suggest that bronchodilation after exercise was blocked by propranolol. Submaximal minute ventilation was significantly reduced with both drugs ($p < 0.05$), a result noted by others,[23] with the reduction with propranolol significantly greater than that with guanadrel sulfate ($p < 0.005$).

These data suggest that propranolol, in the dosages given, had adverse effects on cardiopulmonary function during exercise, compared with an equally effective antihypertensive action of guanadrel sulfate. Also of interest were the lower fasting plasma glucose values before and immediately after exercise with guanadrel sulfate, compared with placebo, suggesting that this drug may have favorable effects on carbohydrate metabolism. With guanadrel sulfate therapy, subjects also had a significant reduction in total serum cholesterol from placebo-baseline values (−16 mg/dl, $p < 0.05$), whereas therapy with propranolol was associated with significantly increased triglyceride levels (+85 mg/dl, $p < 0.05$). Previously, one of us[27] reported that guanadrel sulfate produced a significant decrease in cholesterol levels when added to diuretic therapy. Those data support the current findings.

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Comparison of Ambulatory Left Ventricular Ejection Fraction and Blood Pressure in Systemic Hypertension in Patients With and Without Increased Left Ventricular Mass

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To evaluate the effects of long-standing systemic hypertension on left ventricular (LV) function during daily activities, ambulatory radionuclide monitoring of LV ejection fraction (EF) and blood pressure was performed during exercise and other structured activities in 31 hypertensive patients. Patients were divided into 3 groups based on the absence of LV hypertrophy (group 1 [n = 16], LV mass 107 ± 12 g/m²), presence of LV hypertrophy without electrocardiographic changes (group 2 [n = 10], LV mass 141 ± 8 g/m²) and LV hypertrophy with associated electrocardiographic changes (group 3 [n = 5], LV mass 158 ± 9 g/m²). The groups were similar with respect to age, baseline medication, treated and untreated blood pressure, resting EF and treadmill exercise time. Patients in group 3 had the longest history of hypertension. Peak filling rate was normal in group 1 (2.9 ± 0.4 end-diastolic volume/s), but reduced at rest in groups 2 (2.4 ± 0.4) and 3 (2.1 ± 0.3). Patients in group 1 had normal EF responses to exercise and mental stress testing, as well as during routine ambulatory activities. Patients in group 2 had a blunted EF response to exercise, and those in group 3 had a significantly abnormal response. Both group 2 and 3 patients demonstrated abnormal EF responses to mental stress, as well as cold pressor testing in association with significant increases in mean arterial pressure and marked reduction in diastolic filling rate. Decreases in EF were also observed during routine patient monitoring in 3 group 3 patients and 4 group 2 patients. These events were associated with significantly increased blood pressure. The present study demonstrates that transient LV dysfunctions may accompany excursions of blood pressure that occur during activities when LV hypertrophy complicates hypertension.

(Am J Cardiol 1991;67:597–603)

From the University of Pittsburgh, Pittsburgh, Pennsylvania. This work was supported in part by Ciba-Geigy Corporation, Summit, New Jersey. Manuscript received October 16, 1990; revised manuscript received and accepted November 5, 1990.

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The presence of systemic hypertension has been shown to be a harbinger of cardiovascular morbidity and mortality,[1,2] which may be more pronounced if left ventricular (LV) hypertrophy is present.[3-5] Although LV systolic function is usually normal or supranormal at rest in these patients, diastolic function has often been shown to be impaired.[6-8] Several recent studies have suggested that LV systolic function may become abnormal during exercise or activities associated with increased afterload.[9-11] Whereas the mechanism for abnormal systolic function in hypertension is unknown, it may be related to inadequate LV filling or possibly impaired coronary reserve or myocardial contractile performance abnormalities that accompany increased LV mass.[12,13] The effect of long-standing hypertension on LV function during the performance of daily activity has not been defined. To evaluate such effect, ambulatory radionuclide monitoring of LV ejection fraction (EF) and blood pressure were performed during both exercise and other structured activities in 31 untreated hypertensive patients with and without LV hypertrophy.

METHODS

Patient population: Asymptomatic patients with hypertension (n = 35) but without diabetes mellitus, active cigarette smoking history, or family history of coronary artery disease, were screened from the Hypertension Clinic at Presbyterian-University Hospital and the Veterans Administration Medical Center after a protocol was approved by the Institutional Review Board for Biomedical Research and the Radiation Safety Committee. All were men (86% white, 14% black), mean age ± standard deviation 52 ± 10 years, and all had been taking at least 1 antihypertensive medication (7 patients were taking 2 medications). Forty-eight percent of patients were taking angiotensin-converting enzyme inhibitors, 23% calcium antagonists, 19% diuretics, 16% β blockers and 13% other medications. All patients were withdrawn from medication and were free from medications for 2 weeks before evaluation. Patients with a blood pressure <150/90 mm Hg after the 2-week washout period were excluded from further evaluation. Electrocardiograms were obtained in all patients; those with evidence of left bundle branch block or prior myocardial infarction were also excluded. After routine screening

31 patients were evaluated. Two others were not included because they had inadequate radionuclide studies, and 3 had suboptimal echocardiograms. Patients underwent a routine M-mode and 2-dimensional echocardiogram, and measurements were obtained of septal and posterior wall thickness and LV internal dimensions according to the Penn convention. LV mass was calculated by the formula of Devereux and Reicheck (LV mass (g) = 1.04 [(LV dimension + posterior wall thickness + ventricular septal thickness during diastole)^3 − (LV diastolic dimension)^3] − 13.6), and was normalized to body surface area.[14] LV hypertrophy was diagnosed if the LV mass exceeded 134 g/m^2 and was present in 15 patients. Five patients also had electrocardiographic evidence of LV hypertrophy with associated repolarization abnormalities (ST-T-wave changes). Patients were divided into 3 groups based on the absence (group 1) or presence (group 2) of LV hypertrophy and whether there were associated electrocardiographic changes (group 3). All patients underwent exercise treadmill testing with a standard Bruce protocol in the fasting state.

Performance of radionuclide studies: The blood pool was labeled with 25 mCi of 99-m technetium pertechnetate by a modified in vivo technique.[15] Patients then underwent a 32-frame multigated acquisition study performed in the sitting position in the best septal left anterior oblique view. Radionuclide studies were performed with a GE Starcam 300A (GE, Milwaukee, Wisconsin). Standard methods for EF determination from the left anterior oblique view were used, employing threshold and second derivative edge-detection algorithms with a variable region of interest and periventricular background substraction. A density of 200 counts/pixel was obtained over the LV region of interest.

The nuclear vest (Capintec, Inc., Ramsey, New Jersey) was then positioned in the left anterior oblique projection with the aid of the gamma camera, so that the primary radiation detector counted only within the LV region of interest. A second detector monitored activity over the right lung to assess changes in background radioactivity. Nuclear vest studies were supervised by a single experienced physician (WMB). Nuclear vest studies in normal subjects and patients with coronary artery disease have been found to be reliable and reproducible in our lab.[16] A 2-channel electrocardiogram was simultaneously recorded with the nuclear signal in all patients. During exercise, 12-lead electrocardiograms were also recorded at each stage of exercise and at peak. The 2-channel electrocardiogram recorded with the vest has been shown in previous studies to correlate well with changes observed on the 12-lead electrocardiogram.[17] The vest was worn by patients for a mean of 252 ± 22 minutes. Patients were evaluated during quiet sitting, standing, walking, drinking a cup of coffee, reading the newspaper, routine conversation, as well as a group of activities designed to increase heart rate and blood pressure. All patients underwent exercise testing by a Bruce protocol, climbed 2 flights of stairs, and were evaluated during cold pressor testing, isometrics and mental stress testing. Before the end of the study protocol, measurements of LVEF were taken at rest and patients were then placed in front of the gamma camera to check detector position. EF, peak filling rate (end-diastolic volume/s) and ST-segment analysis were performed at 30-second intervals throughout the study. Procedures for review of the study for technical adequacy and the processing of data have been previously described.[16,17] An abnormal vest response was defined as a decrease in EF of ≥5 EF units that persisted for ≥60 seconds. This definition was not used for cold pressor testing because our studies in normal subjects indicate that there generally is a decrease in EF in response to cold exposure. A stable baseline EF was obtained before each provoked maneuver. All data were carefully analyzed to exclude motion or other artifacts. Changes in relative radionuclide stroke and end-systolic volumes are expressed as percent change from baseline.

Blood pressure measurements: Along with radionuclide monitoring, all patients had continuous automatic blood pressure recordings performed (SpaceLabs model 90202, SpaceLabs Inc., Redmond, Washington). Blood pressure recordings with this ambulatory device were correlated with cuff measurements and found to be accurate and reproducible. Blood pressure was obtained at 6-minute intervals along with heart rate (beats/min). A real-time clock on the ambulatory blood pressure monitor was timed to the nuclear vest to correlate changes in EF with changes in blood pressure. Additionally, the device was triggered in a manual mode to obtain blood pressure measurements at the start, peak and completion of all activities. Mean arterial pressure was determined from the automated pressure recordings.

Statistical analysis: The mean ± standard deviation are shown for all variables. To evaluate differences between groups 1 through 3 (group 1, without LV hypertrophy; group 2, with LV hypertrophy but without electrocardiographic changes; group 3, LV hypertrophy with electrocardiographic changes), as well as within groups, analysis of variance for repeated measures was used. When analysis of variance was found to be significant ($p < 0.05$), testing between and within groups was performed with a Student Newman-Kuels test.

RESULTS

Patient characteristics and baseline data: Of the patients who gave informed consent, 31 had complete radionuclide, echocardiographic and blood pressure data that could be evaluated. Patients were divided into 3 groups based on the absence (group 1, n = 16) or presence (group 2, n = 10) of LV hypertrophy and whether there were electrocardiographic changes associated with LV hypertrophy (group 3, n = 5). Patients in group 3 had the greatest LV mass by echocardiography (158 ± 9 g/m^2), but LV mass was increased in both groups 2 and 3 compared with group 1 (107 ± 12 g/m^2). Additionally, patients in group 3 were found to have a longer history of hypertension (16.5 vs 8.8 years in group 1, 11 years in group 2). The groups were simi-

lar with respect to age, baseline medication, blood pressure with and without medication, resting EF and treadmill exercise time. No patient had chest pain or an anginal equivalent on the treadmill and no patient in groups 1 and 2 had electrocardiographic changes with exercise. Patients in group 3 had indeterminate treadmill tests because of baseline electrocardiographic abnormalities. The resting peak filling rate (measured by the vest) was normal in group 1 (2.9 end-diastolic volume/s), but abnormal in groups 2 and 3 (2.4, 2.1 end-diastolic volume/s, respectively).

Response to exercise (Tables I to III): EF response to exercise was significantly different for patients in group 1 than in groups 2 and 3 (Figures 1 and 2). Patients in all 3 groups had a similar increase in mean arterial blood pressure and heart rate with exercise, but the EF response that was normal in group 1 patients (67 ± 8 to 80 ± 6% at peak) was blunted in group 2 and absent in group 3 (Tables I to III). In all group 1 patients, EF increased normally with exercise, compared with only 4 of 10 group 2 patients and only 1 of 5 group 3 patients. Relative end-systolic volume decreased in group 1 (−13%) at peak exercise, but did not change substantially in groups 2 and 3 (−5%, 1%). Peak filling rate increased significantly during exercise in group 1 (2.9 to 3.8 end-diastolic volume/s), but did not change significantly from baseline in the other groups (group 2, 2.4 to 2.7; group 3, 2.1 to 2.3 end-diastolic volume/s at peak, difference not significant for both).

Mental stress testing (Tables I to III): Patients underwent mental stress testing with serial arithmetic and a Stroop mental stress test. The response in group 1 patients was normal with a small increase in EF to 71%. In group 1 patients, heart rate and blood pressure response was less than observed with exercise, but was significantly increased from baseline values. Both groups 2 and 3 demonstrated markedly abnormal responses to mental stress testing with decreases in EF (group 2, −57 ± 8%; group 3, −51 ± 9% at peak) and significant increases in mean arterial pressure, which in most cases were above that obtained at peak exercise levels (Figure 3). This was seen in 7 of 10 group 2 patients and in all 5 group 3 patients. Changes in EF either followed or occurred at the same time as the increases in blood pressure. Relative end-systolic volume increased in groups 2 and 3 at peak mental stress testing

TABLE I Group 1—No Left Ventricular Hypertrophy (n = 16)

	Baseline	Peak Exercise*	Mental Stress	Cold Pressor*
Ejection fraction (%)	67 ± 8	80 ± 6	71 ± 5	61 ± 6
Mean arterial pressure (mm Hg)	114 ± 8	136 ± 12	130 ± 11*	134 ± 9
Peak filling rate (end-diastolic volume/s)	2.9 ± 0.4	3.8 ± 0.5	3.3 ± 0.3*	2.5 ± 0.6
Heart rate (beats/min)	72 ± 16	138 ± 22	80 ± 12	94 ± 12
Relative stroke volume (%)	—	22 ± 11%	8 ± 6%	−12 ± 7%
Relative end-systolic volume (%)	—	−13 ± 7%	−5 ± 4%	+10 ± 6%

* p <0.05, significant difference from baseline.
% = percent change from baseline.

TABLE II Group 2—Left Ventricular Hypertrophy Without Electrocardiographic Changes (n = 10)

	Baseline	Peak Exercise	Mental Stress	Cold Pressor
Ejection fraction (%)	65 ± 8%	68 ± 7%*	57 ± 8%*	56 ± 9%†
Mean arterial pressure (mm Hg)	116 ± 8.3	138 ± 11†	142 ± 9* †	148 ± 12* †
Peak filling rate (end-diastolic volume/s)	2.4 ± 0.4*	2.7 ± 0.6*	2.1 ± 0.5*	1.9 ± 0.7
Heart rate (beats/min)	75 ± 15	136 ± 17†	79 ± 11	92 ± 14†
Relative stroke volume (%)	—	8 ± 5%	−13 ± 6%†	−15 ± 8%†
Relative end-systolic volume (%)	—	−5 ± 2%*	+10 ± 5%*	+12 ± 7%†

* p <0.05, significant difference group 2 vs group 1; p values determined from analysis of variance and Student Neuman-Kuels test.
† p <0.05, significant difference from baseline; % = percent changes from baseline.

TABLE III Group 3—Left Ventricular Hypertrophy with Electrocardiographic Changes (n = 5)

	Baseline	Peak Exercise	Mental Stress	Cold Pressor
Ejection fraction (%)	63 ± 9	62 ± 6%*	51 ± 9%*	49 ± 8* †
Mean arterial pressure (mm Hg)	117 ± 9	135 ± 13%†	149 ± 11* †	153 ± 15* †
Peak filling rate (end-diastolic volume/s)	2.1 ± 0.3*	2.3 ± 0.4*	1.8 ± 0.4*	1.8 ± 0.5
Heart rate (beats/min)	74 ± 11	132 ± 15†	81 ± 9	94 ± 13†
Relative stroke volume (%)	—	3 ± 4%	−20 ± 8%†	−23 ± 9%†
Relative end-systolic volume (%)	—	1 ± 5%*	15 ± 6%* †	19 ± 8%* †

* p <0.05, significant difference group 3 vs group 1; p values determined from analysis of variance and Student Neuman-Kuels test.
† p <0.05, significant difference from baseline; % = percent change from baseline.

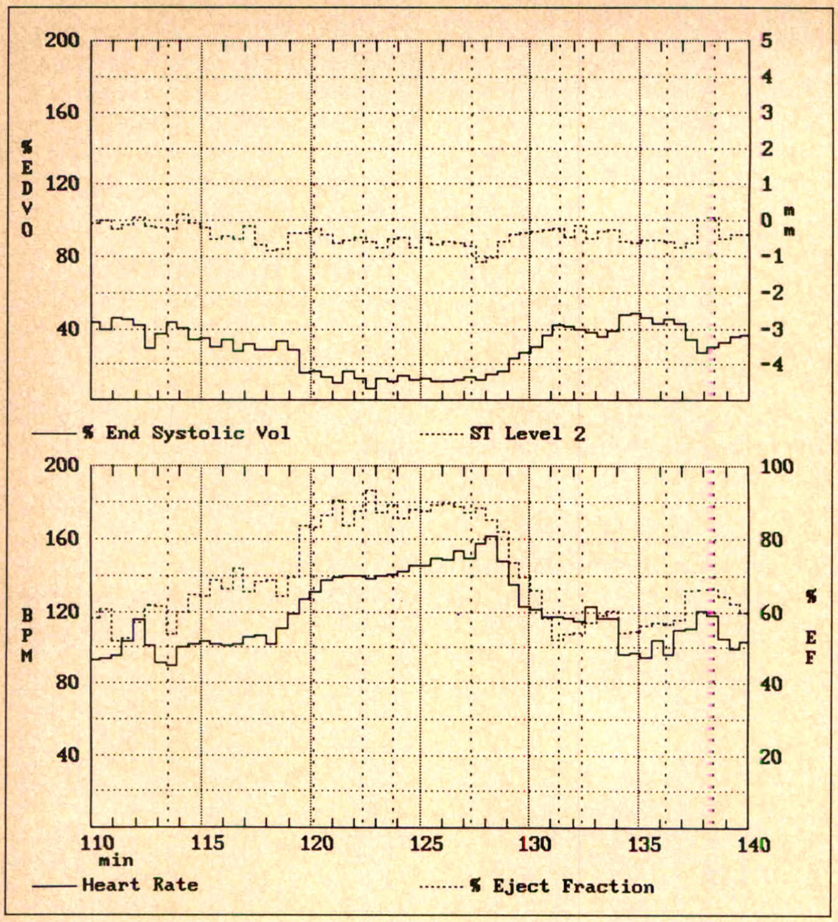

FIGURE 1. Ambulatory vest recording from a group 1 patient during exercise treadmill testing. *Top panel, dotted line* is the measurement of ST-segment changes; *bottom solid line,* percent end-systolic volume (EDVO). *Bottom panel, top dotted line,* ejection fraction (EF) (%); *bottom solid line,* heart rate (BPM). *First vertical line* at 113 minutes represents the start of exercise and at 127 minutes the peak of exercise. Ejection fraction increased from 60 to 88% at the peak of exercise with an increase in heart rate to 158 beats/min. The ST segments do not change during exercise, but the percent end-systolic volume decreases substantially during the exercise test. This would be a normal physiologic response to exercise.

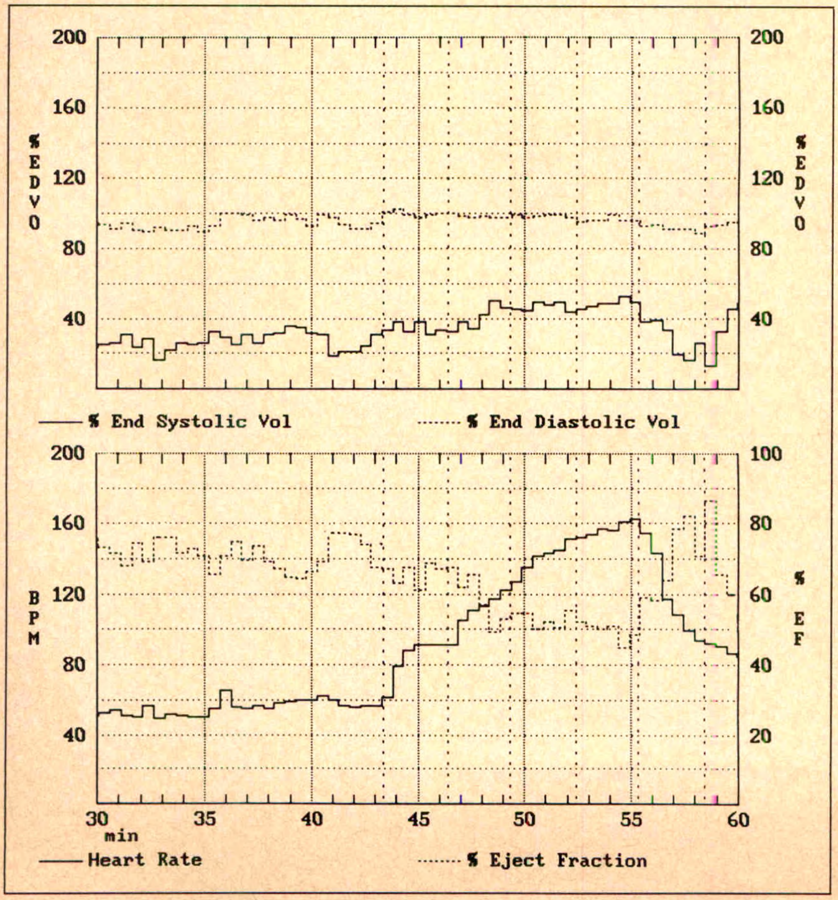

FIGURE 2. Ambulatory vest recording from a group 3 patient during exercise testing. *Top panel,* percent end-diastolic volume (EDVO) *(dotted line)* and percent end-systolic volume *(solid line); bottom panel,* ejection fraction (EF) (%) in the *dotted line* and heart rate (BPM) in the *solid line. Vertical line* at 43 minutes represents the start of exercise and after 55 minutes the peak of exercise. Ejection fraction decreased from 70 to 49% at peak exercise. Heart rate increased from 58 to 160 beats/min. Compared with patients in group 1, end-diastolic volume shows minimal change and end-systolic volume increased significantly during exercise. This response is abnormal, and in a patient with coronary artery disease would be typical of myocardial ischemia.

(10 ± 5%, 15 ± 6%, respectively), which largely accounted for the decline in EF. No symptoms or electrocardiographic changes were noted during mental stress testing. Peak filling rate increased from baseline in patients without LV hypertrophy but, as with effort, decreased in both groups 2 and 3.

Cold pressor testing: Hand immersion in ice water for at least 1 minute constituted a cold pressor test. Although all 3 groups demonstrated a decline in EF, this was most marked in group 3 patients whose EF decreased from 63% at baseline to 49% at peak cold exposure. Although heart rate response was similar in all groups, mean arterial pressure increased dramatically in groups 2 and 3 (148 ± 12, 153 ± 15 mm Hg, respectively) compared with the response in group 1 (134 ± 9 mm Hg). The decrease in EF was primarily due to increased end-systolic volume in each of the groups. For all groups peak filling rate decreased during cold pressor testing from baseline, and although the decrease was greatest in group 3 (1.8 ± 0.5 end-diastolic volume/s), overall differences did not achieve statistical significance. Patients in groups 1 and 2 had no electrocardiographic changes, but 4 of 5 patients in group 3 developed increased asymptomatic ST-segment depression during cold pressor testing.

Other findings during ambulatory monitoring: Isometric testing with a dynamometer handgrip device (Jamar) paralleled the responses seen with mental stress testing. EF response was normal in group 1, but in 6 of 10 group 2 patients and in 4 of 5 group 3 patients EF decreased in association with marked increases in mean arterial pressure. Decreases in EF (≥5 EF units) were also observed on 12 occasions during the patient monitoring period, in 3 group 3 and in 4 group 2 patients. No spontaneous decreases in EF were observed in any group 1 patient except during micturition in 1 patient. All spontaneous decreases in EF were associated with marked elevations in mean arterial pressure comparable to that seen with mental stress or cold pressor testing. On each of these occasions the elevation in blood pressure preceded or occurred at the same time as the decrease in EF. In no instance were there associated electrocardiographic changes or cardiac symptoms. These events were unassociated with changes in heart rate, and the decreases in EF were similar to what was observed with other activities. On 2 occasions EF decreased while patients were upset on the telephone, 3 instances during conversation that caused emotional excitement, 2 episodes while patients were drinking coffee and 5 while walking stairs.

DISCUSSION

The present study examined the relation of the ambulatory blood pressure to LV function in patients with hypertension and varying levels of LV hypertrophy.

Systolic ventricular function in hypertension: Numerous studies have examined the use of exercise testing as a means of evaluating LV reserve in hypertension.[9-11,18-20] Whereas most studies have found normal exercise ejection function in hypertensive persons with-

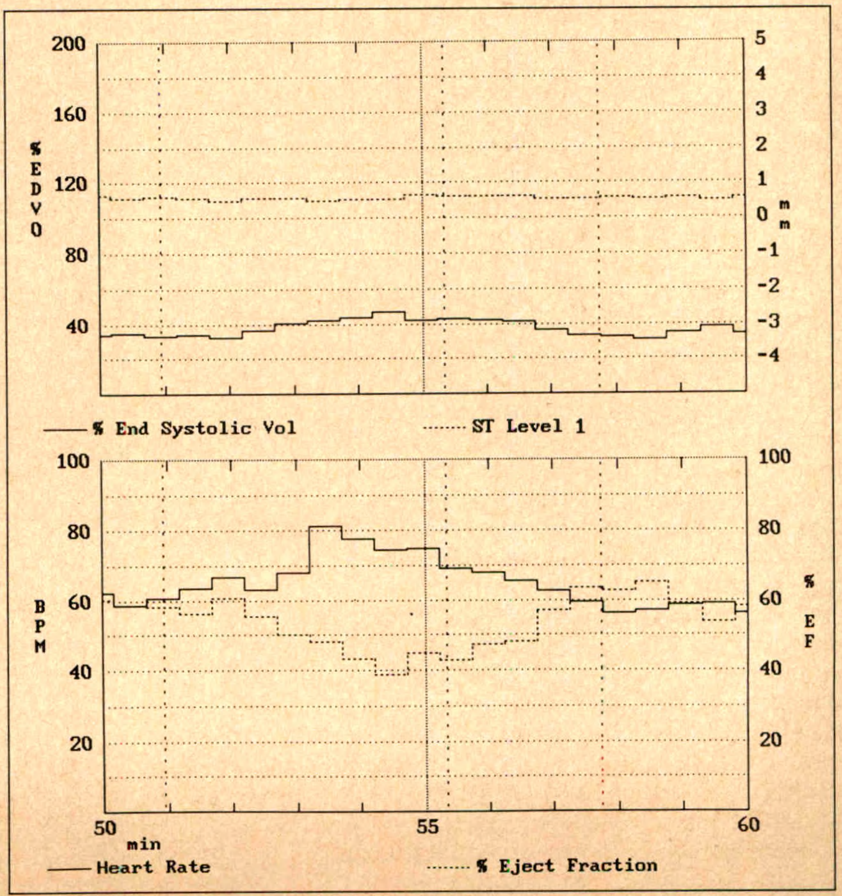

FIGURE 3. The same group 3 patient as in Figure 2 is shown during mental stress testing with serial arithmetic. *Top panel,* ST-segment level is represented by the *dotted line,* and percent end-systolic volume (EDVO) in the *solid line. Bottom panel,* heart rate is the *solid line* (BPM) and ejection fraction (EF) (%) the *dotted line. Vertical line* at 51 minutes represents the start of serial arithmetic, at 55 minutes the task was completed and complete recovery to baseline by 58 minutes. Ejection fraction decreased substantially from 60 to 39% at peak testing. Heart rate increased from 62 to 81 beats/min during mental stress testing. There was no change on the electrocardiogram and there was an increase in percent end-systolic volume, similar to that observed with exercise.

out LV hypertrophy (as observed in our study), Miller et al[10] observed abnormal EF responses in >50% of their hypertensive patients. In their study, LV mass was not assessed by echocardiographic criteria for LV hypertrophy, but only on the electrocardiogram. Tubau et al[9] demonstrated that systolic impairment is common during exercise in patients with increased LV mass. In that study, as LV mass increased, there was a decrease in the peak systolic pressure/end-systolic volume index during exercise consistent with impaired myocardial contractility. Boudoulas et al[21] also reported abnormalities of the preejection period and LV ejection time associated with increased LV mass, as well as decreased velocity of circumferential shortening during effort. It is also known that in patients with advanced LV hypertrophy the contractile state of the ventricle may be impaired even at rest.[22] Because our patients manifested a graded EF response to exercise, when considered in relation to LV mass, the present findings are consistent with previous studies documenting altered systolic functional reserve in parallel with LV mass increase in hypertension. Since the altered EF response paralleled the increase in ventricular mass, "normal" afterload dependance of ejection cannot alone account for the present findings.

Diastolic ventricular function: Although systolic function is generally well preserved at rest in hypertensive patients, previous studies have shown that alterations of relaxation and filling function are common.[6-8,23] Diastolic abnormalities may be the earliest manifestation of high blood pressure in the heart and, when marked, may be associated with the development of congestive heart failure even with normal systolic function.[24,25] In our study, peak filling rate was normal in patients without hypertrophy (group 1), but was markedly abnormal in patients in groups 2 and 3 (<2.5 end-diastolic volume/s), despite normal resting systolic function and arterial pressure. These results are in agreement with previous studies[7,8,23] of diastolic function in hypertensive subjects, and suggest that as with ejection, filling is progressively impaired as LV mass increases. Filling rates tended to decline further when EF decreased. Such declines in filling rate may simply have followed altered ejection function[26] as a response to increased hemodynamic load (see later). Alternatively, impaired filling may have caused inadequate augmentation of end-diastolic volume during stress; thus, a decline in EF occurred at increased afterload.[27] Last, the finding of increased end-systolic volume as the mechanism of reduced EF during stress raises the possibility that altered ventricular filling reflects underlying disease of hypertrophied myocardium.

Role of increased mean arterial pressure: Activities that provoked more significant increases in mean arterial pressure uncovered greater degrees of LV dysfunction. For example, during cold pressor testing, the most marked EF decreases occurred in group 3, where the greatest increases in mean arterial pressure occurred. Mental stress testing, associated with lesser increases in blood pressure compared with cold pressor testing, caused abnormal EF responses only in patients with LV hypertrophy (groups 2 and 3).

In addition to laboratory activities, other routine activities also caused transient decreases in EF in patients with increased LV mass. Furthermore, such EF responses only occurred when the mean arterial pressure was elevated. Over the short monitoring period, such abnormal responses were relatively common during types of daily activities (walking stairs, phone conversation, drinking coffee, active discussion) that one might not suspect would impair ventricular function.

Study limitations: Although the present study group was carefully screened, one cannot exclude the possibility of associated epicardial coronary artery disease. Thallium imaging was not performed since several studies suggest that interpretation of thallium imaging in this population is difficult and that false-positive scans are common.[28,29]

The nuclear vest that was used in this study has recently been shown to be a useful method for evaluating LV function in patients during ambulatory activities.[30,31] The vest provided a high temporal resolution determination of EF and filling rate that could be obtained at 30-second intervals, and closely correlated with blood pressure changes. Studies in patients with coronary artery disease have suggested that changes in LVEF measured with the vest are reliable, reproducible and useful in identifying patients with myocardial ischemia.[17] Normal subjects have been evaluated with this technique but physiologic responses of hypertensive patients are unknown.

Significance of the findings: Whereas LV hypertrophy represents an adaptive process to the presence of high blood pressure, it has clearly been shown to indicate a poor prognosis.[4] The basis of such altered prognosis remains unclear and episodic, or chronic ischemia due to impaired coronary flow reserve[12,13,32] may be contributors. However, by whatever mechanism, the present studies reveal that stressor settings that elevate blood pressure, even transiently, may adversely affect ventricular performance in systole and diastole in the laboratory or during daily life. Such findings may help explain the poor outcomes in patients with LV hypertrophy due to hypertension, and further support the mandate for optimal blood pressure control in high-risk persons.

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Abnormal Baroreflex Control of Heart Rate in Decompensated Congestive Heart Failure and Reversal After Compensation

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Congestive heart failure (CHF) causes impairment of baroreflex control of heart rate (HR). To determine if this derangement is reversible, the cardiac chronotropic control was assessed in 10 patients with class IV chronic CHF of various etiologies before and after compensation achieved by bed rest, salt restriction, diuretics and vasodilators. Mean time between the 2 studies was 15 ± 3 days. The management was modified 3 days before the second autonomic evaluation, so as to reestablish the same diet and pharmacologic conditions of the previous study. Compensation led to significant reduction in symptom-based class, body weight, and pulmonary and systemic congestion. Mean ± standard error of the mean HR responses (beats/min) before and after compensation were, respectively: (1) to atropine (0.04 mg/kg): 10 ± 2 and 27 ± 2 ($p < 0.01$); (2) to handgrip (30% maximum capacity, 1 minute): 9 ± 2 and 19 ± 3 ($p < 0.005$); (3) to head-up tilt (5 minutes): 4 ± 3 and 20 ± 4 ($p < 0.005$). Mean ± standard error of the mean baroreflex sensitivity (ms/mm Hg) of RR responses to phenylephrine and amyl nitrate–induced changes in systolic pressure was, respectively, in each condition: phenylephrine, 0.9 ± 0.2 and 8 ± 2.3 ($p < 0.05$); amyl nitrate, 0.3 ± 0.2 and 4.1 ± 1.1 ($p < 0.05$). A significant correlation between improvement in HR responses to atropine and tilt and changes in body weight was obtained. These findings show a reversible component of impaired baroreflex control of HR in severe CHF, possibly due to its congestive effects.

(Am J Cardiol 1991;67:604–610)

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Profound abnormalities in the neurohumoral control of the circulatory system occur in congestive heart failure (CHF).[1-4] Several derangements have been shown in the adrenergic[5-11] as well as in the parasympathetic[12-13] efferent limbs of the autonomic circulatory control, both in patients and in experimental animals with CHF. The severity of the functional autonomic impairment correlates well with the curtailment of cardiac reserve, as shown by studies in various symptomatic classes.[7,12,14]

There is scant evidence that some of these disturbances may be, at least in part, reversible after recovery of CHF. In humans and in experimental animals, diminished urinary and plasma catecholamine levels[8] and recovery of depleted myocardial stores of norepinephrine occur with reversal of CHF.[15] In human CHF treated with converting enzyme inhibitors, some increase in baroreflex sensitivity was also demonstrated.[16] In other studies, reflex chronotropic responses to hypotension, but not to hypertension, were restored 8 months after reversal of a high-output model of CHF in the dog.[17] Orthotopic heart transplantation in humans led to early improvement in the receptor sinus node and plasma norepinephrine responses to both hypertension and hypotension,[18] and to dynamic exercise.[19] The adrenergic excitatory state typically associated with CHF was also reversed when cardiac function was restored by surgical correction of congenital heart disease.[20] Although the mechanisms responsible for the autonomic dysfunction associated with CHF are not fully understood, blunting of baroreflexes may be due to structural[17] or functional[18] derangements in the afferent and efferent component limbs of the reflex arc. Abnormal interaction with reflexes arising from volume-overloaded cardiopulmonary receptors has also been advanced as a possible mechanism.[3,21] Moreover, circulatory congestion and increased vascular sodium content may be responsible for alterations in the mechanical properties of the arterial wall at the baroreceptor site.[22] Acute administration of a vasodilator that reduces both afterload and preload to patients with CHF was associated with significant changes in the arterial baroreflex sensitivity, which correlated well with concomitant decreases in left ventricular filling pressures.[23]

A previous study in 2 patients has shown that clinical compensation of CHF, i.e., simple alleviation of its congestive effects by conventional medical management could reverse the impairment of the autonomic control of heart rate (HR).[23] The purpose of the present investi-

TABLE I Clinical Catheterization of Patients Studied

Pt. No.	Age (yr) & Sex	Etiology	Duration of CHF	Episodes of Decomp.	Pre- and Postcompensation Medication (daily dosage) D (mg)	F (mg)	KCl (g)	Medication During In-Hospital Compensation (daily dosage) D (mg)	F (mg)	KCl (mg)	Other	(mg)
1	24F	DC	18 mo	4	0.25	40	—	0.25	80	—	S	100
2	29M	DC	1 mo	1	0.25	40	1.8	0.25	80	1.8	—	—
3	30M	DC	4 mo	2	0.25	40	—	0.25	120	1.8	—	—
4	36F	DC	9 yrs	7	0.25	40	—	0.25	120	1.8	I	75
5	52M	DC	7 mo	1	0.25	80	—	0.25	120	—	A	5
6	56M	DC	8 yrs	4	0.25	40	—	0.25	80	1.8	—	—
7	40M	HCVD	6 mo	1	0.25	40	1.8	0.25	120	—	—	—
8	48M	HCVD	3 mo	1	0.25	40	1.8	0.25	80	1.8	—	—
9	39M	CAD	2 yrs	5	0.25	80	1.8	0.25	120	1.8	IS	40
10	41F	CAD	5 mo	2	0.25	40	—	0.25	120	1.8	—	—

A = amiloride; CAD = coronary artery disease; D = digoxin; DC = dilated cardiomyopathy; Decomp. = decompensation; F = furosemide; HCVD = hypertensive cardiovascular disease; I = indoramin; IS = isosorbide dinitrate; KCl = potassium chloride; S = spironolactone.

TABLE II Characterization of Clinical Compensation Achieved by Medical Treatment of Congestive Heart Failure

Pt. No.	Days Between Studies	NYHA Class D	NYHA Class C	BW (kg) D	BW (kg) C	Pulmonary Congestion D	Pulmonary Congestion C	X-Rays CTR D	X-Rays CTR C	Systemic Congestion D	Systemic Congestion C	Echocardiographic Dimension (mm) LVd D	LVd C	LVFS (%) D	LVFS (%) C	RVd D	RVd C	LA D	LA C
1	16	IV	II	60	51	2	0	0.70	0.53	E,H,J	—	63	61	16	18	25	20	39	36
2	12	IV	II	62	58	3	1	0.57	0.44	E,H,J	—	48	45	29	40	26	17	34	35
3	4	IV	II	55	50	3	0	0.51	0.44	E,H,J	—	60	64	15	17	24	26	42	39
4	18	IV	II	56	50	3	0	0.57	0.53	E,H,J,A	—	55	56	20	20	24	22	48	41
5	13	IV	III	71	58	2	0	0.50	0.44	E,H,J	H	68	62	15	19	15	17	45	25
6	12	IV	III	53	50	2	0	0.59	0.50	E,H,J	—	75	71	15	18	17	17	52	41
7	10	IV	II	80	65	3	1	0.61	0.47	E,H,J	—	62	59	16	24	27	19	46	43
8	35	IV	III	78	65	3	1	0.59	0.49	E,H,J,A	—	—	—	—	—	—	—	—	—
9	19	IV	II	62	61	3	0	0.54	0.49	E,H,J	—	62	63	19	20	32	30	38	40
10	8	IV	II	71	71	2	0	0.56	0.55	E,H,J	H	60	50	30	34	19	21	41	42
Mean	15			65	58			0.57	0.49			61	59	19	23	23	21	43	38
± SEM	3			3	2			0.02	0.01			3	3	2	3	2	2	2	2
Significance				p <0.01				p <0.01				NS		p <0.05		NS		p <0.05	

A = ascites; BW = body weight; C = compensation; CTR = cardiothoracic ratio; E = edema; H = hepatomegaly; J = raised jugular pressure; LA = left atrium; LVd = left ventricular dimension; LVFS = left ventricular fractional shortening; NS = not significant; NYHA = New York Heart Association; RVd = right ventricular dimension; SEM = standard error of the mean; 0 = normal; 1 = upper lobe congestion; 2 = hilar shadowing; 3 = interstitial edema (Kostup classification).

gation was to extend these observations, evaluating the sympathetic and parasympathetic regulation of the sinus node, in class IV CHF, before and after its clinical compensation.

METHODS

Patients: Ten patients (7 men and 3 women, mean age 40 years) in sinus rhythm admitted to our hospital with New York Heart Association class IV decompensated CHF comprise the study population. CHF was due to several conditions (Table I). The duration of CHF averaged 27 months (range 1 month to 8 years) and the number of episodes of overt CHF requiring hospitalization ranged from 1 to 7. All patients signed an informed consent before entry into the study protocol, which was approved by the ethics committee of our medical school university hospital.

Study protocol: The protocol comprised 2 studies of the autonomic circulatory control. The first was performed at entry, on day 0, when all patients had given a history of symptomatic class IV deterioration and showed signs of severe pulmonary and systemic congestion on physical examination. The second evaluation of autonomic function was performed after compensation of CHF, as defined by several criteria (Table II): (1) symptomatic class reduction; (2) diminished physical and radiologic signs of congestion; (3) body weight loss; (4) x-ray cardiothoracic ratio reduction; and (5) echocardiographic evidence of chamber size reduction. The time that elapsed between the 2 studies averaged 15 ± 3 days.

All patients were given digoxin and furosemide therapy at entry. The digoxin dosage was maintained unaltered throughout the investigation, but in several patients the therapeutic regimen was changed after the first study (Table I). A moderately strict bed rest was established, and the patients were maintained on a diet with 70 to 80 mEq/day of sodium. Three days before the second autonomic evaluation, after compensation had been achieved, the treatment was modified so as to establish the same diet and pharmacologic conditions that were present during the first study.

Methods for assessing autonomic function: All studies were performed during the morning in a temperature-regulated room (22 to 24°C), with the patients fasting overnight and with daily medications withheld.

In the decompensated state, because several patients were too ill to undergo every test or because of technical problems, only 5 patients underwent all tests: upright tilt, handgrip, Valsalva maneuver, amyl nitrate, phenylephrine and atropine. In the other patients, the autonomic evaluation was limited to the assessment of HR responses to tilt, handgrip and atropine.

Tilt test: After 30 minutes in the supine position, patients were passively tilted to a 70° head-up position on a table that allowed a change in posture in <3 seconds.[24]

Isometric exercise: Each patient was acquainted with a calibrated spring-type dynamometer[25] and the maximum voluntary contraction of the dominant arm was determined. Five minutes later baseline recordings were obtained in the supine position, and then the patient performed a sustained 30% handgrip for 1 minute.

Atropine test: Atropine sulphate (0.04 mg/kg) was given intravenously at the rate of 0.25 mg/min in the supine position.

Phenylephrine, amyl nitrate and Valsalva tests: These tests were performed before atropine injection in the supine position. An indwelling catheter was inserted into an antecubital vein, and a Cournand 20G needle placed after local anesthesia into the brachial artery. An intravenous bolus of 25 to 400 μg of phenylephrine hydrochloride was followed by 10 ml of saline flushing, to induce a 20- to 30-mm Hg increase in systolic pressure. For the amyl nitrate test, the content of 2 ampoules of 0.2 ml was inhaled during 2 respiratory cycles, so as to achieve a decrease in systolic pressure of 10 to 30 mm Hg below baseline. For the Valsalva maneuver, the expiratory pressure was held for 20 seconds at 40 mm Hg.

Continuous recording of the electrocardiogram at 5 mm/s was obtained during the tilt, handgrip and atropine tests. Blood pressure and oral pressure were recorded at 25 mm/s during the phenylephrine, amyl nitrate and Valsalva tests.

Data analysis: HR responses to head-up tilt were measured at 10 seconds and 5 minutes in the upright position.[24] The chronotropic responses to handgrip were analyzed at 1 minute of isometric effort. Changes in HR induced by atropine were measured 5 minutes after the intravenous infusion. In these tests HR changes were measured with regard to immediate pretest baseline values.

The data obtained with the phenylephrine test were analyzed according to the method described by Smyth et al.[26] In each patient only injections producing regression lines with significant correlation coefficients ($p < 0.05$) were considered. The slopes of 3 to 4 lines were averaged to provide a mean baroreflex sensitivity for each patient. The amyl nitrate test was analyzed according to the technique described by Pickering et al.[27] Similar to the phenylephrine method, baroreflex sensitivity values were obtained by plotting successive diminishing systolic pressure values and the corresponding next cycle RR intervals. An average of 3 tests was obtained for each patient.

Blood pressure changes during the Valsalva maneuver were used to assess the effects of compensation. The chronotropic changes observed were measured as the Valsalva ratio, i.e., the longest RR interval during the poststrain phase IV, divided by the shortest RR interval recorded during the expiratory effort.[28] Mean values of 3 tests were obtained for each patient.

A paired Student's *t* test was used to compare mean responses of the group in the decompensated and in the compensated state of CHF, for all autonomic tests. The same test was used to assess statistical significance of chronotropic responses elicited by each test with regard to baseline values of HR. Changes in the HR responses were correlated to corresponding individual changes in body weight, cardiothoracic ratio and echocardiographic chamber dimensions, by the nonparametric Spearman test.

RESULTS

All values reported in the text, tables and figures are mean ± standard error of the mean for the group, in each condition or test.

Responses to tilting: Before compensation of CHF, tilt caused a HR increase from 110 ± 6 to 115 ± 4 beats/min at 10 seconds in the upright position (+5%, difference not significant) and to 113 ± 3 beats/min at 5 minutes (+3%, difference not significant). After compensation, HR in the supine position averaged 90 ± 4 beats/min, increasing to 104 ± 3 beats/min at 10 sec-

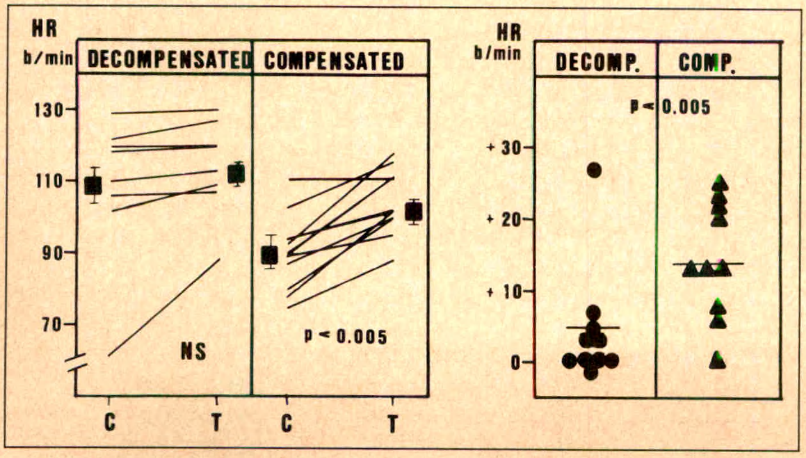


FIGURE 1. Early (10 seconds) heart rate (HR) responses to 70° head-up tilt. *Left panel,* absolute individual heart rate values during control (C) and tilt (T), with respective mean ± standard error of the mean for both decompensated (DECOMP.) and compensated (COMP.) states of congestive heart failure. *Right panel,* the individual chronotropic changes elicited by tilt are shown in each state. *Horizontal bars* indicate mean values for the heart rate responses to tilt. NS = not significant.

onds of tilt (+15%, p <0.005) and to 110 ± 3 beats/min at 5 minutes in the upright posture (+20%, p <0.001). Figures 1 and 2 show that HR increments were significantly larger after compensation than in the decompensated state during both the early (10 seconds) and late (5 minutes) phases of the postural test. Neither significant changes in blood pressure nor vasovagal fainting was seen in any of the patients in each condition of CHF. Average systolic and diastolic blood pressure values were 141 ± 11/95 ± 7 mm Hg in the supine position and 144 ± 11/97 ± 8 mm Hg at 5 minutes of tilt in the decompensated state; these values are greater (p <0.05) than those observed after compensation: 122 ± 5/83 ± 5 mm Hg in the supine position and 122 ± 6/85 ± 5 mm Hg after 5 minutes in the upright position.

Responses to handgrip: Handgrip caused significant HR changes: during decompensation, it increased from 110 ± 3 to 119 ± 3 beats/min (+8%), and after compensation it increased from 89 ± 4 to 110 ± 4 beats/min (+23%). Mean increase after compensation was significantly larger than in the decompensated state (+19 and +9 beats/min, respectively, Figure 3).

Responses to atropine: Significant (p <0.001) positive chronotropic responses were induced in both phases of CHF. Before compensation, mean HR increased from 108 ± 5 to 118 ± 4 beats/min and after compensation it increased from 89 ± 4 to 116 ± 3 beats/min. The average increase of +10 beats/min before compensation was significantly smaller than that of +27 beats/min after compensation (Figure 4).

Responses to phenylephrine and amyl nitrate: A markedly attenuated baroreflex slope was seen in the decompensated state of CHF, for both phenylephrine (0.95 ± 0.22 ms/mm Hg) and amyl nitrate (0.31 ± 0.2 ms/mm Hg). A striking increase in baroreflex sensitivity occurred after compensation, to 8.02 ± 231 ms/mm Hg with phenylephrine, and to 4.68 ± 1.07 ms/mm Hg with amyl nitrate (Figure 5).

Responses to the Valsalva maneuver: Before compensation of CHF, the typical "square-wave" behavior of blood pressure was seen in all patients.[28] No significant chronotropic changes were detected. After compensation, a striking trend toward normalization of blood pressure responses was seen (Figure 6), which depicts the phases of decreasing pressure during and immediately after the expiratory effort, and the poststrain overshoot usually seen in normal subjects. In this condition, HR increased during strain, and was reduced immediately after the expiratory effort. The Valsalva ratio increased from 1.02 ± 0.01 during decompensation to 1.53 ± 0.26 after compensation (p <0.05).

Correlation between changes in the indexes of compensation and corresponding improvement in reflex chronotropic responses: A generally poor correlation was found between changes in HR responses to each test and corresponding individual changes in body weight, cardiothoracic ratio and echocardiographic di-

FIGURE 2. Late (5 minutes) heart rate (HR) responses to 70° head-up tilt. *Left panel,* absolute individual HR values during control (C) and tilt (T), with respective mean ± standard error of the mean for both decompensated (DECOMP.) and compensated (COMP.) states of congestive heart failure. *Right panel,* the individual chronotropic changes elicited by tilt are shown in each state. *Horizontal bars* indicate mean values for HR responses to tilt. NS = not significant.

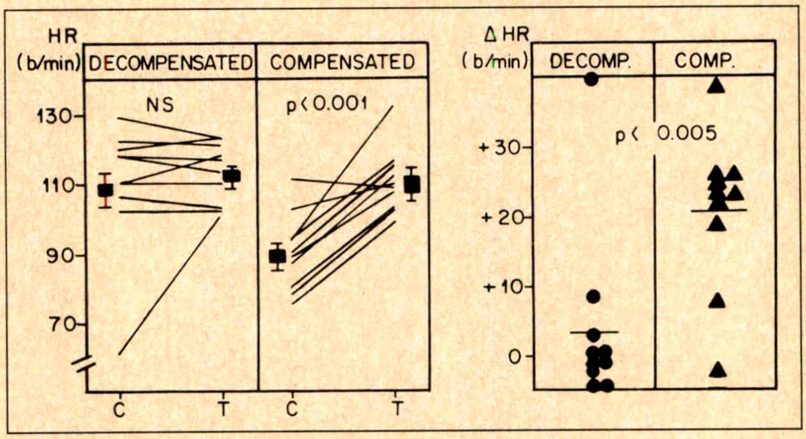
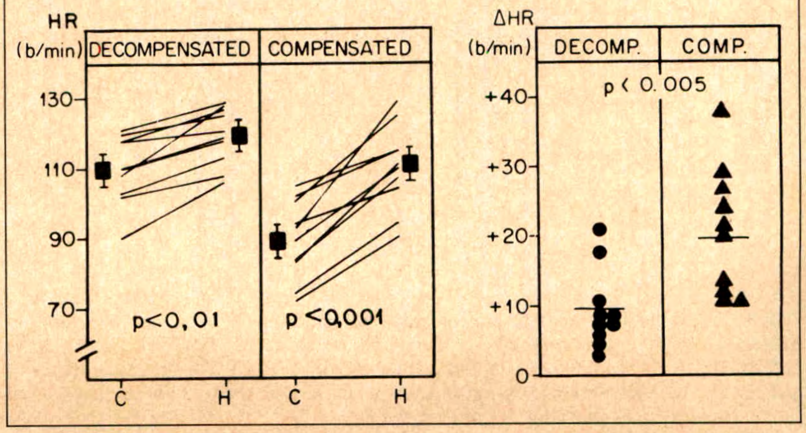


FIGURE 3. Heart rate (HR) responses to hand grip (H)—30% of maximum voluntary capacity for 1 minute. *Left panel,* absolute individual heart rate values during control (C) and hand grip, with respective mean ± standard error of the mean for both decompensated (DECOMP.) and compensated (COMP.) states. *Right panel,* the individual chronotropic changes elicited by hand grip are shown in each state. *Horizontal bars* indicate mean values.



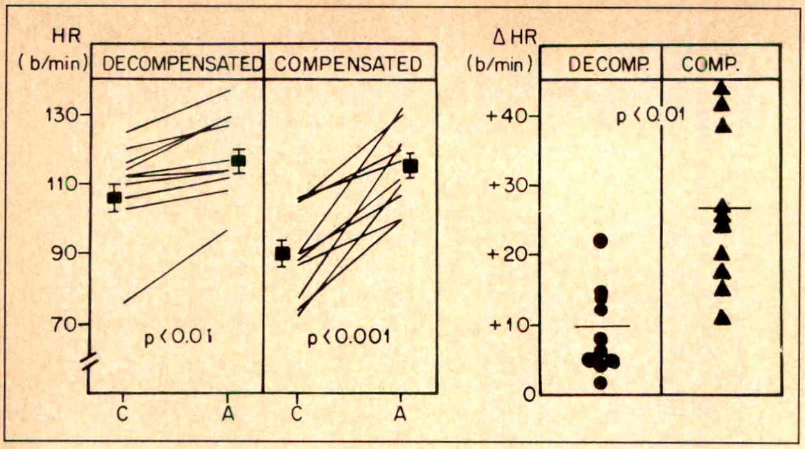


FIGURE 4. Heart rate (HR) responses to intravenous atropine, 0.04 mg/kg body weight. *Left panel*, absolute individual HR values during control (C) and after atropine (A), with respective mean ± standard error of the mean for both decompensated (DECOMP.) and compensated (COMP.) states. *Right panel*, the individual chronotropic changes induced by atropine are shown in each state.

mensions, taking these parameters as continuous variables. The only significant correlations refer to improvement in chronotropic responses elicited by atropine and 5 minutes of head-up tilt and the corresponding reductions in body weight (Figure 7).

DISCUSSION

This study provides evidence that striking improvement in the depressed baroreflex control of HR occurs when compensation of class IV CHF is achieved through conventional medical therapy. The augmented HR responses to late upright tilt and to the strain of Valsalva maneuver indicate a better sympathetic control of HR after compensation of CHF. A concomitant improvement in the parasympathetic cardiac system is reflected by increased baroreflex sensitivity to transient hypertension and hypotension induced by pharmacologic interventions. An increased tonic vagal restraint on the sinus node, in the compensated state, is revealed by augmented HR responses to atropine. In addition, a clear resetting to lower range was seen in the baseline HR after compensation; a significant bradycardia was seen after compensation during the phase IV overshoot of the Valsalva maneuver, and a more prominent vagal withdrawal is disclosed during the early (10 seconds)

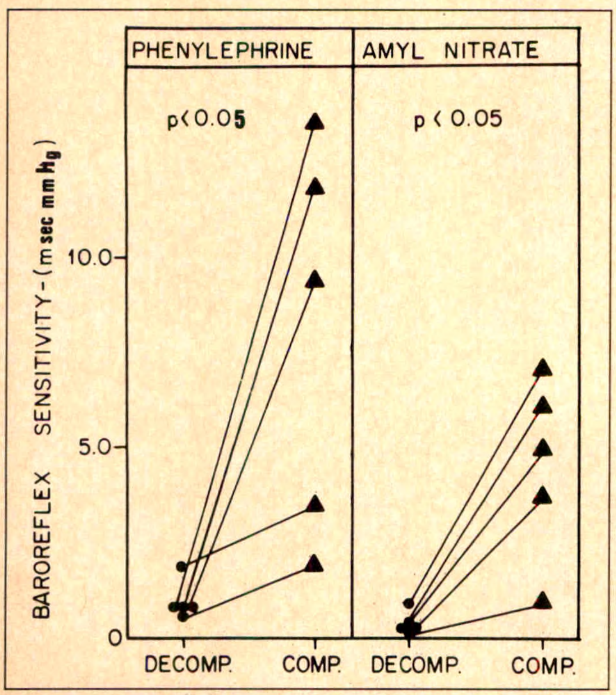


FIGURE 5. Individual baroreflex sensitivity values obtained with phenylephrine and amyl nitrate during decompensation (DECOMP.) and compensation (COMP.) of congestive heart failure. The individual sensitivity values were obtained according to the methods described in references 26 and 27.

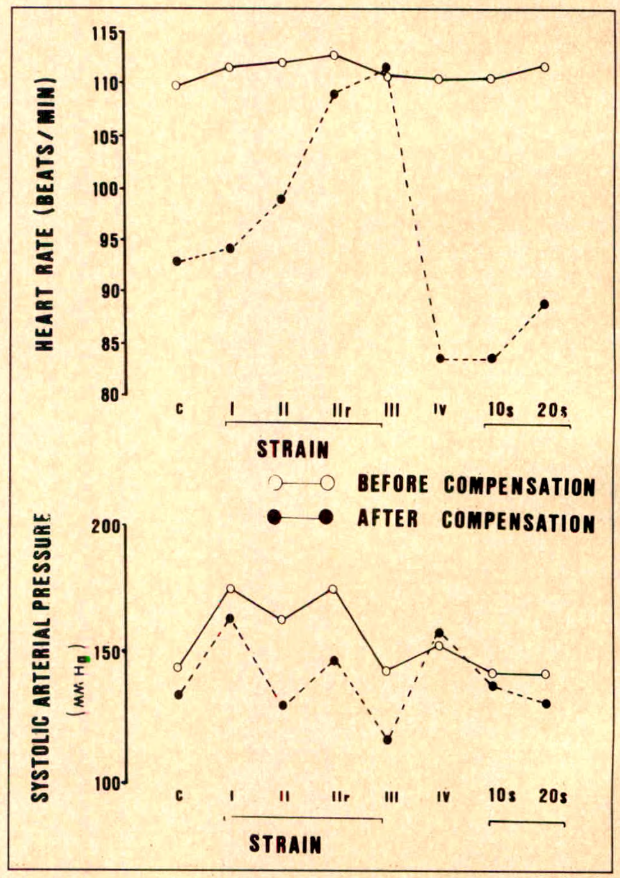


FIGURE 6. Heart rate *(top panel)* and systolic arterial pressure *(bottom panel)* responses to the Valsalva maneuver—40 mm Hg for 20 seconds. Values represented correspond to the average obtained in 5 patients before and after compensation of congestive heart failure. Phases I to IV of the Valsalva maneuver are shown as defined in reference 28. C = control.

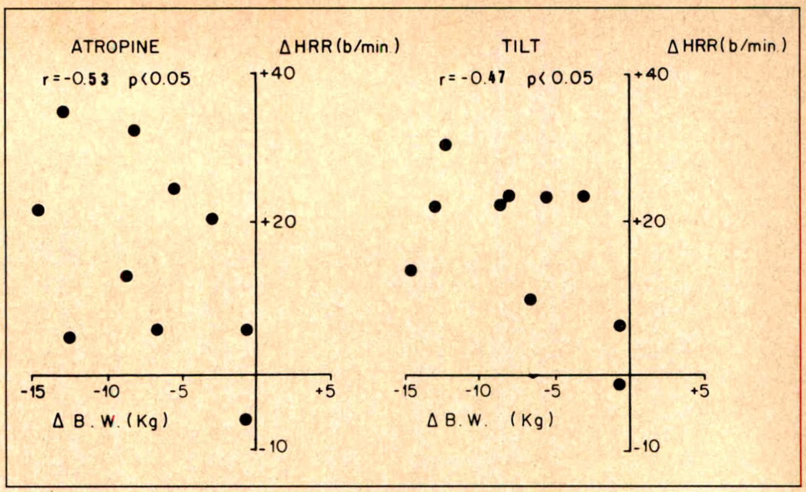


FIGURE 7. Correlation between the individual changes in heart rate responses (HRR) to atropine and tilt, and corresponding variations in body weight after compensation of congestive heart failure. B.W. = body weight.

response to tilt.[24] Finally, although predominantly mediated by vagal efferent pathways,[25] the increased chronotropic responses to handgrip after compensation also reflect an improved sympathetic control of HR.

The present findings are consistent with results of previous studies showing that the autonomic impairment was greater in patients with more severe symptoms.[12,14] However, no studies are available reporting a deterioration of the autonomic control of the heart, in the same group of patients, as CHF worsens. The present findings are unique in that only class IV decompensated patients had an autonomic evaluation performed before and after compensation of CHF. One could speculate that a good correlation might exist between the effects of compensation on HR changes elicited and the respective individual changes in clinical indexes of congestion. However, significant correlation was only found regarding body weight reduction, and changes in HR responses to the orthostatic stress and atropine. Lack of significant correlations regarding responsiveness to other tests may be due to the small number of patients whose response was assessed.

A study in patients with orthotopic cardiac transplants provided direct evidence of an early and complete recovery of baroreflex-mediated responses of the recipient atrial sinus node.[18] These results led to the conclusion that neurohumoral rather than structural abnormalities were responsible for the impairment of baroreflex responses in CHF.[18] Our own results support this hypothesis, showing that an important component of the baroreflex derangement in cardiac failure is reversible early after compensation of CHF. Alleviation of congestion probably causes decreased sodium and water content of the arterial wall; this could increase the sensitivity of the arterial baroreflex by providing more favorable conditions of distensibility and extent of distortion of the receptors during pressure changes.[13,22] In fact, reversible structural changes in aortic baroreceptors were shown in dogs with chronic volume overload.[3]

In conscious dogs subjected to acute volume overload, marked blunting of arterial baroreflex responses was interpreted as possibly caused by overriding effects resulting from excessive stimulation of low-pressure receptors.[21] Excessive stimulation of low-pressure receptors could cause reduced arterial baroreflexes in human CHF and, conversely, a better setting of interaction between the 2 systems would prevail after compensation. However, it is not possible to reconcile this hypothesis with evidence that CHF induced by a variety of experimental procedures leads to impairment instead of overactivation of atrial receptor responses.[3,29] Moreover, reversal of chronic high-output failure caused an increase in sensitivity of atrial receptors, accompanied by regression of cardiac dilatation.[3]

A possible mechanism for improved HR control could be reversible down-regulation at the efferent receptors site, particularly in regard to adrenergic responses.[9] The contribution of this factor cannot be assessed by data from the present study.

In contrast to previous studies of patients with heart transplants,[18,19] this investigation showed partial reversibility of baroreflex abnormalities associated with reversal of congestive phenomena, without recovery of myocardial function. Thus, an essentially severely diseased heart remained. This phenomenon is similar to studies in heterotopic cardiac transplantation showing that the recipient heart had normal chronotropic responses to active orthostasis, isometric exercise and Valsalva maneuver 6 to 15 months after transplantation.[30] In this model of heart transplantation, the functional recovery of circulatory conditions is dependent on a normally contracting but denervated donor heart, whereas the recipient heart remains diseased, even though largely alleviated of the previous burden represented by adverse ejection and filling conditions (at least partly due to the abnormal adrenergic and humoral activation).

In conclusion, the present study provides evidence that a reversible component of the impairment of baroreflex control of HR is essentially dependent on the congestive effects of CHF.

Acknowledgment: We thank the nurses and technicians of the cardiac catheterization laboratory for technical assistance, and Rosa Maria Pereira Coquely for typing the manuscript.

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Doppler Echocardiographic Study of Porcine Bioprosthetic Heart Valves in the Aortic Valve Position in Patients Without Evidence of Cardiac Dysfunction

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To study the natural history of the hemodynamic performance of bioprosthetic heart valves, Doppler echocardiograms were recorded in a group of clinically stable patients at 2 and 5 years after replacement of native aortic valves with bioprosthetic valves. Eighteen patients completed a 2-year and 26 patients a 5-year follow-up examination. The effective orifice areas of identical models of bioprosthetic valves (Hancock II) were determined in vitro in a left-sided heart pulse duplicator system. In vivo Doppler-derived effective orifice areas were compared with the in vitro measurements for the same valve size. At both the 2- and 5-year follow-up examinations, the Doppler-derived effective orifice area was significantly less than the in vitro area ($p < 0.0001$ at each interval). Ten of 16 valves evaluated serially decreased >0.20 cm^2 in the Doppler-derived effective orifice area between studies. The mean decrease in effective orifice area in valves evaluated serially was 0.25 ± 0.29 cm^2 ($p < 0.005$). The peak transaortic gradient increased from 21 ± 6 to 27 ± 8 mm Hg ($p < 0.01$). The mean transaortic gradient increased from 12 ± 4 to 15 ± 7 mm Hg ($p < 0.05$). It is concluded that serial Doppler echocardiographic studies demonstrate a deterioration in the hemodynamic performance of bioprosthetic valves over time in patients with no symptoms or signs of valvular dysfunction and that Doppler echocardiography may be useful for identifying subclinical bioprosthetic valvular dysfunction.

(Am J Cardiol 1991;67:611–615)

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Doppler echocardiography allows accurate noninvasive determination of peak and mean transvalvular gradients across both native and bioprosthetic valves.[1–3] Valve areas calculated by Doppler echocardiography correlate well with valve areas measured at catheterization.[1,4] Using Doppler methods, it may be possible to obtain serial evaluations of the hemodynamic performance of bioprosthetic valves in order to identify dysfunction before the development of clinical symptoms. Thus, this study compares the effective orifice areas determined by Doppler and in vitro methods and prospectively evaluates serial hemodynamic changes in a group of patients without clinical evidence of bioprosthetic valve dysfunction.

METHODS

Patients were enrolled in this study at the time of valve replacement with a Medtronic Hancock II porcine xenograft.[5] They were asked to return for follow-up evaluations at 2 and 5 years after aortic valve replacement. Evaluations involved history, physical examination, and 2-dimensional and Doppler echocardiograms. Patients were enrolled if they were clinically stable, in New York Heart Association functional class I or II, and had a physical examination by a cardiologist consistent with normal valve function. The 2-year examinations were designated as "early" follow-up and the 5-year examinations as "late" follow-up. Of 49 patients undergoing a Hancock II aortic valve replacement from 1984 to 1986 at the Brigham and Women's Hospital, 18 patients agreed to early follow-up and 26 to late follow-up. Six of the initial 49 patients died within 5 years after valve implantation and did not participate in this study. Thromboembolism occurred in 1 patient enrolled in the study.

Two-dimensional echocardiograms, recorded with patients in the left lateral decubitus position, were obtained with a Hewlett Packard 77020 AC/AR phased array ultrasonoscope device using a 2.5-MHz transducer. Parasternal short- and long-axis, apical 4- and 5-chamber and second right intercostal space images were recorded. Pulsed-wave Doppler sampling of left ventricular outflow tract flow was recorded from the apical 5-chamber view, with the sample volume beneath the aortic valve leaflets. Continuous-wave Doppler sampling of transaortic flow was recorded from the apical position.

TABLE I Characteristics of Patients and Bioprostheses in Study

	Early	Late
No. of pts.	16	26
Heart rate (beats/min)	71.4 ± 12.0	69.1 ± 12.3
Stroke volume (ml)	79.8 ± 9.3	76.2 ± 13.3
Cardiac output (liters/min)	5.6 ± 1.2	5.2 ± 1.2
	No. of Pts.	
Aortic valve size		
21 mm	1	2
23 mm	13	12
25 mm	4	12

TABLE II In Vitro Effective Orifice Areas for Hancock II Bioprostheses

Aortic Valve Size (mm)	Effective Orifice Area (cm^2)
21	1.46 ± 0.10
23	1.81 ± 0.15
25	2.07 ± 0.18

Values are mean ± standard deviation.

Pulsed-wave Doppler sampling of the left ventricular outflow tract from the apical 5-chamber position was used to evaluate aortic insufficiency in the early study; pulsed-wave and Doppler color-flow mapping were used to evaluate aortic insufficiency in the late study. Aortic insufficiency was semiquantitated with the methods of Ciobanu,[6] Perry,[7] and their co-workers.

An off-line digitizing analysis program, Cardiology Workstation (GTI Freeland Medical Division), was used to analyze echocardiographic data. The left ventricular outflow tract diameter was measured from the parasternal long-axis view in systole; a mean of 3 consecutive beats was used. Left ventricular outflow tract and transaortic Doppler flow velocity profiles were digitized by an investigator blinded to the valve sizes. For each Doppler measurement, 5 spectral envelopes were averaged and analyzed for patients in sinus rhythm; 10 spectral envelopes were analyzed for those in atrial fibrillation. Peak and mean gradients were calculated with the modified Bernoulli equation, as previously described.[3]

The stroke volume was calculated as the product of the left ventricular outflow tract cross-sectional area and the velocity time integral (VTI) of the left ventricular outflow tract. The effective orifice area was determined as follows[4,8]: aortic effective orifice area = stroke volume/VTI of transaortic flow.

Pulsatile flow experiments were conducted with saline solution in the left-sided heart pulse duplicator system of the Georgia Institute of Technology. A detailed description of the pulse duplicator system and aortic flow chamber has been published previously.[9,10] New Hancock II bioprostheses of various sizes were placed in the system, with physiologic conditions as follows: (1) heart rate of 70 beats/min, (2) systolic time of 300 ms and diastolic time of 560 ms, (3) mean aortic pressure of 90 to 100 mm Hg, and (4) cardiac output in the range of 2.0 to 7.5 liters/min. Pressure drops across the valve were measured with Statham physiologic pressure transducers (P23 ID) interfaced to Honeywell bridge amplifiers (218-I). The pulsatile volumetric flow rate was monitored with a Carolina Medical electromagnetic flowmeter (FM 501) and a 25-mm (inner diameter) cannulating flow probe (EP 680). The analog signal outputs from the bridge amplifiers and electromagnetic flowmeter were interfaced to an Apple II Plus microcomputer via a 16-channel analog-to-digital convertor.[11] These signals were digitized at the rate of 500 to 1,000 samples per second and analyzed on-line by the microcomputer for ≥10 consecutive cardiac cycles.

From the pressure drop measurements, the effective orifice area was estimated according to the following equation: effective orifice area = $Q_{rms}/(51.6 \cdot \sqrt{P})$, where $\sqrt{P}$ is the square root of the mean systolic or diastolic pressure drop across the valve in mm Hg, and Q_{rms} is the root mean square of the systolic or diastolic flow rate (cm^3/s).[10–12] The effective orifice area was averaged over cardiac outputs of 2.0 to 7.5 liters/min, representing the mean ± standard deviation of 40 sample points for each valve size.[11]

Statistics: Mean values ± standard deviation were determined for stroke volume, mean gradients, peak gradients and effective orifice areas. Comparisons were made between these variables with paired Student's *t* tests. Comparisons of the difference between in vitro and Doppler-derived effective orifice areas were also made with paired Student's *t* tests. A p value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics: The 26 patients returning for late follow-up were aged 59 ± 18 years (range 27 to 89) and 20 were men. Early follow-up occurred at 25 ± 5 months and late follow-up at 59 ± 7 months after valve replacement. Of 16 patients completing both 2- and 5-year examinations, the time interval between studies was 34 ± 1 months. At late follow-up, 24 patients were in New York Heart Association class I and 2 were in class II.

Bioprosthetic aortic regurgitation was observed by Doppler echocardiography in 5 of 18 patients (28%) during the early examination and in 9 of 26 patients (35%) during the late examination (difference not significant). Seven patients had mild (1+) and 2 had moderate (2+) aortic regurgitation at late follow-up.

The mean heart rate of patients at early and late follow-up was 71 ± 12 and 69 ± 13 beats/min, respectively (Table I). Mean cardiac output was 5.7 ± 1.2 liters/min at early follow-up and 5.3 ± 1.1 liters/min at late follow-up. Thus, the mean patient heart rate did not differ significantly from that used in the in vitro testing (70 beats/min). Mean cardiac output at both follow-up times was in the middle of the range of cardiac outputs used in the in vitro experiments.

The in vitro effective orifice area increased as the size of the bioprosthetic valve ring increased (Table II). The Doppler-derived effective orifice area was compared to the in vitro area of valves of the same ring size.

The Doppler-derived effective orifice areas at both early and late follow-up were significantly smaller than those determined in vitro (Figure 1, A and B). At early follow-up, the mean difference was 0.21 ± 0.20 cm^2 ($p < 0.0001$). Three years later, the difference between the in vitro and Doppler-derived effective orifice areas was 0.41 ± 0.32 cm^2 ($p < 0.0001$).

Ten of 16 patients (63%) with serial studies had a decrease of >0.20 cm^2 in the effective orifice area and only 1 patient had an increase of >0.20 cm^2. The mean decrease in effective orifice area for all valves was 0.25 ± 0.29 cm^2 ($p < 0.005$) (Figure 2). The aortic transvalvular peak and mean gradients both increased over time. The peak gradient increased from 21 ± 6 to 27 ± 8 mm Hg ($p < 0.01$) (Figure 3). The mean aortic gradient increased from 12 ± 4 to 15 ± 7 mm Hg ($p < 0.05$) (Figure 4). For patients with serial examinations, the stroke volume between the 2 examinations did not significantly differ; the early stroke volume was 80 ± 9 ml and the late stroke volume was 76 ± 14 ml ($p = 0.27$).

DISCUSSION

This study used Doppler echocardiographic methods to evaluate bioprosthetic valve function 2 and 5 years after porcine aortic valve replacement. In these patients without clinical evidence of valve dysfunction, a decrease in the effective orifice area was accompanied by an increase in transvalvular gradients. Previous studies

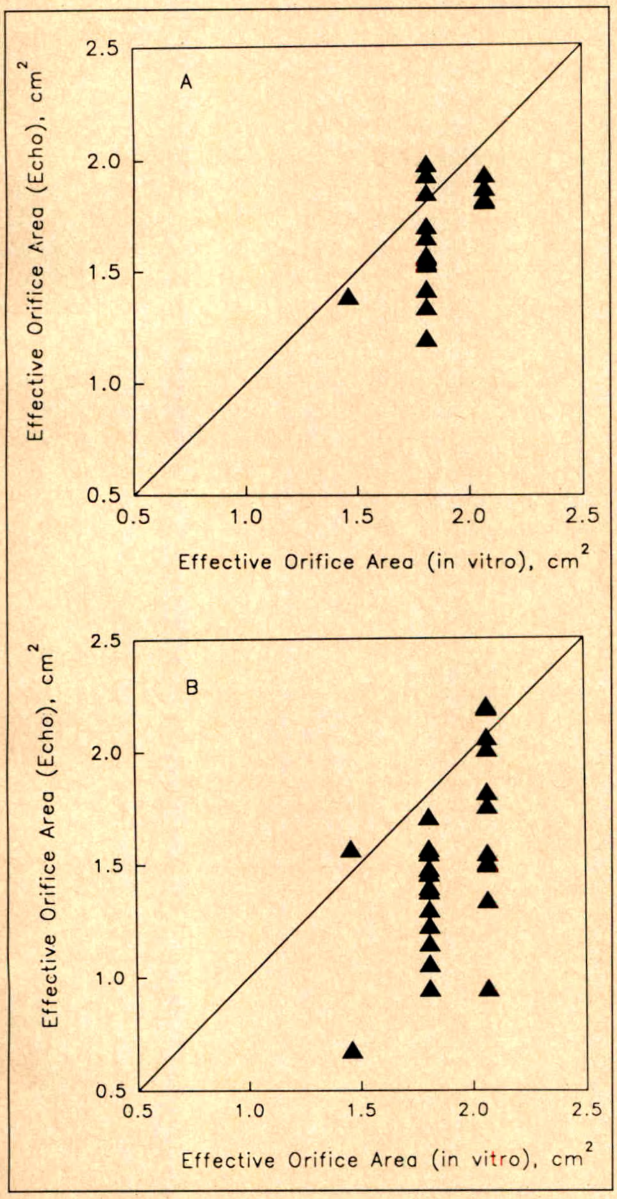

FIGURE 1. *A*, effective orifice area in vivo determined by Doppler echocardiography (Echo) versus effective orifice area in vitro at 2 years after valve replacement. *B*, effective orifice area in vivo determined by Doppler echocardiography versus effective orifice area in vitro at 5 years after valve replacement. *Diagonal line* is the line of identity.

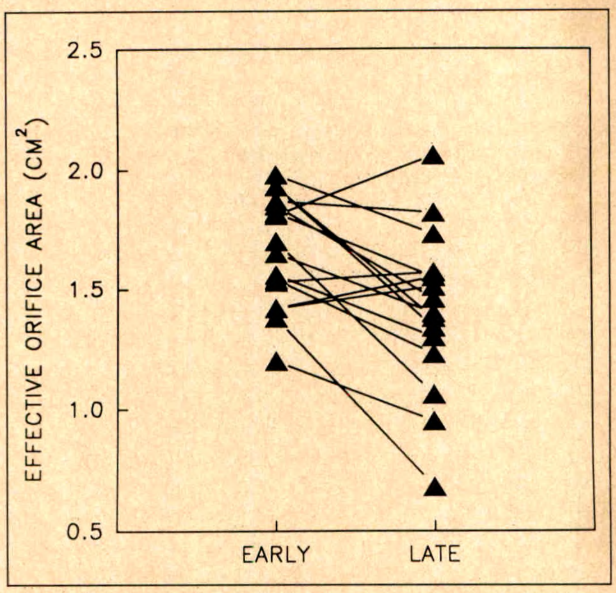

FIGURE 2. Effective orifice areas in vivo as determined by serial Doppler echocardiographic studies at 2 (early) and 5 (late) years after valve replacement.

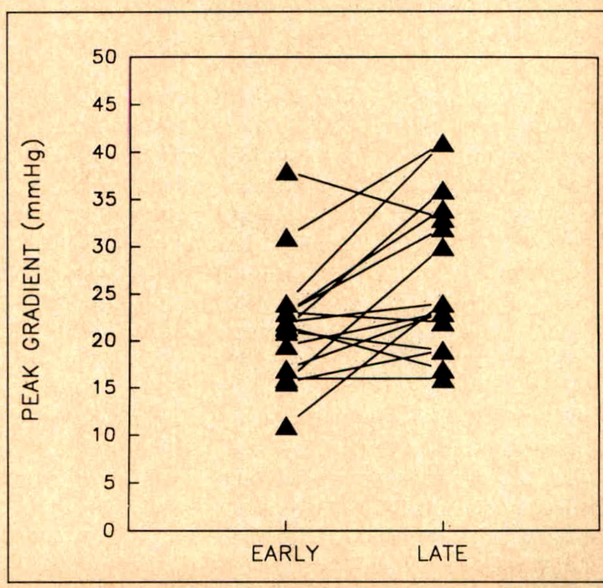

FIGURE 3. Peak transvalvular gradients as determined by serial Doppler echocardiographic studies at 2 (early) and 5 (late) years after valve replacement.

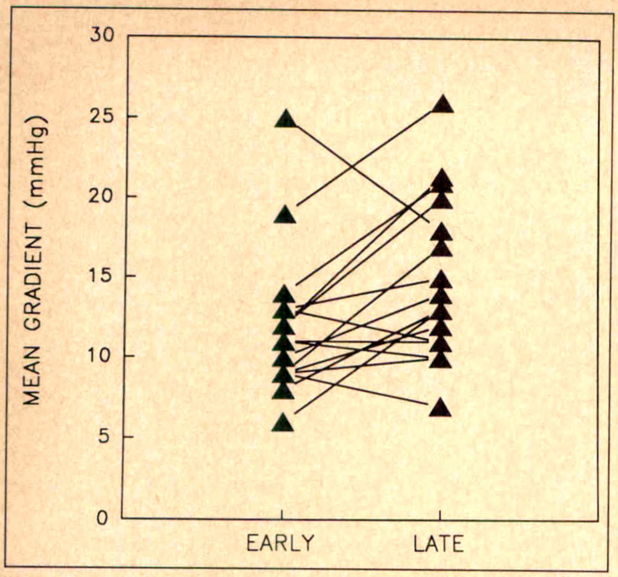

FIGURE 4. Mean transvalvular gradients as determined by serial Doppler echocardiographic studies at 2 (early) and 5 (late) years after valve replacement.

have evaluated gradients in bioprosthetic valves at various times after replacement.[13,14] These series did not systematically study patients at a uniform time after operation.[14,15] Assessing "normal" transvalvular gradients at variable times may affect the results, as some investigators noted high gradients across some valves in the early postoperative period.[16] These data demonstrate that the valve gradient and area depend not only on the type and size of valve but also on the time from insertion. This decrease in prosthetic effective orifice area was noted 2 to 5 years after operation in a population that was doing well clinically and before the usual appearance of clinical valve dysfunction (8 to 12 years after operation).[17]

The Doppler-derived effective orifice area was significantly smaller than the in vitro orifice area 2 and 5 years after operation. This difference may reflect the fact that valvular changes, thickening and calcification occurred since valve implantation, and probably represents early valvular degeneration. Alternatively, the difference could be secondary to errors in the in vitro or in vivo calculations of orifice area. Systematic underestimation of the orifice area by Doppler echocardiography could arise from inadequate measurement of the left ventricular outflow tract diameter, errors in the assumption that the left ventricular outflow tract is circular, or incident angle errors in measuring the velocities by ultrasound. These issues could be partially resolved by recording an adequate Doppler echocardiogram shortly after implantation. Unfortunately, the continuity equation was not in frequent use at the time of valve implantation in these patients and adequate Doppler echocardiograms were not recorded until 2 years after operation. Although no echocardiographic data are available for Hancock II valves early after implantation, a recently performed study of a new bioprosthetic valve demonstrated a good correlation between in vitro and Doppler-derived areas obtained shortly after implantation.[18]

Serial changes in orifice area and gradients were not secondary to changes in stroke volume and most likely represent early valvular degeneration. This degeneration may occur as collagen in the leaflets is disrupted, allowing binding of calcium to the valve at points of maximal stress and changing stiffness and bending properties of the leaflets.[19–21] The percentage of patients with regurgitant lesions was not significantly different between echocardiographic studies. Two patients developed moderate aortic regurgitation. In 1 of these, the effective orifice area increased from 1.80 to 2.06 cm^2, possibly secondary to an increase in stroke volume. Increases in stroke volume can lead to increases in effective bioprosthetic valve area.[22] Regurgitant lesions, often due to leaflet tears, may develop more acutely than stenotic lesions and lead to sudden decompensation; this may explain why progressive regurgitation was not observed in this stable population 5 years after valve replacement.

Although only patients with Hancock II bioprostheses were examined in this study, there is no evidence that the leaflets of this bioprosthesis degenerate more rapidly than other currently available bioprostheses. It is reasonable to apply the basic principles of this study to the evaluation of other types of bioprostheses. Serial determinations of effective orifice areas may allow assessment of the durability of these valves before clinical manifestations of valve failure develop.

Acknowledgment: We thank Peter A. Chevalier, PhD, Charles Dowd and Diana Lutz, RN, of the Medtronic Heart Valve Division, Minneapolis, Minnesota, for helpful discussions and support throughout this study. We also thank Anna Mae Forsberg, RN, and the Brigham and Women's Hospital noninvasive cardiology technicians for assistance with the study.

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Clinical and Doppler Echocardiographic Follow-Up After Percutaneous Balloon Valvuloplasty for Aortic Valve Stenosis

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Percutaneous balloon valvuloplasty has been shown to increase the aortic orifice area and to improve clinical symptoms. However, there are only few data concerning long-term results after balloon valvuloplasty. In this study, 36 patients (11 men, 25 women, mean age 75 ± 8 years) were followed after balloon valvuloplasty for a period of up to 18 months by means of clinical parameters and repeated Doppler echocardiographic measurements after 1, 3, 6, 12 and 18 months. Invasive measurements revealed a decrease of the systolic peak gradient from 78 ± 24 to 38 ± 13 mm Hg (p <0.001), and an increase in the aortic orifice area from 0.58 ± 0.23 to 0.93 ± 0.2 cm² (p <0.001). The Doppler echocardiographic approach revealed that the maximal instantaneous gradient decreased from 96 ± 26 to 67 ± 22 mm Hg (p <0.001). The aortic orifice area increased from 0.49 ± 0.16 to 0.73 ± 0.21 cm² (p <0.001). Three patients (8%) died in the hospital. After hospital discharge, 16 patients (44%) died and 8 patients (22%) underwent successful aortic valve replacement after a mean follow-up of 8 ± 6 months. Nine patients (25%) were alive after a follow-up period of 18 months. Seven of these (19%) remained clinically improved. During follow-up, the Doppler echocardiographic results revealed a continuous trend toward the preprocedural severity of the aortic valve stenosis. Progression of restenosis assessed by Doppler echocardiographic measurements was accelerated in the group of patients who subsequently died or underwent repeat balloon valvuloplasty or aortic valve replacement.

(Am J Cardiol 1991;67:616–621)

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Since the introduction of percutaneous balloon valvuloplasty of valvular aortic stenosis in 1986,[1] this technique was initially favored as an alternative therapy to the surgical approach.[2–6] Balloon valvuloplasty of severe aortic stenosis has been proposed mainly for elderly patients considered at high risk for valve replacement.[7,8] Initial hemodynamic results of this technique were promising. In most patients, invasive measurements obtained immediately after balloon valvuloplasty indicated a significant increase in the aortic valve orifice area, which subsequently resulted in a marked improvement of clinical symptoms. During follow-up, restenosis seemed to occur frequently.[9–15] However, incidence and extent of restenosis determined by repeat Doppler echocardiography over a longer follow-up period had only been described in a few studies, particularly in selected patients.[14–19]

In the present study, consecutive patients were followed for periods of 18 months after balloon valvuloplasty of the aortic valve in order to assess data on the mortality, morbidity, clinical symptoms and the time course of restenosis determined by Doppler echocardiographic data.

METHODS

Patients: From February 1987 to July 1988, 36 patients with severe degenerative calcific aortic valve stenosis underwent percutaneous balloon valvuloplasty. Eleven men and 25 women at a mean age (± standard deviation) of 75.3 ± 7.5 years (range 50 to 91) were studied. All patients were highly symptomatic: 33 of 36 patients (92%) had New York Heart Association [NYHA] functional class III and IV heart failure; 3 patients (8%) were classified in class II. Recurrent syncope had been documented in 10 patients (28%). Twenty-two patients (61%) had severe chest pain.

Technique of percutaneous balloon valvuloplasty: Written consent was obtained from all patients before intervention. Catheterization was performed in 31 patients (86%) under local anesthesia and mild sedation (10 mg of diazepam). In 5 patients (14%), balloon valvuloplasty had to be performed under general anesthesia with endotracheal intubation because of severe heart failure. Exclusion criteria were aortic regurgitation, angiographic grade >II, and 3-vessel coronary artery disease. Of patients included in this study, 1 (3%) had 1-vessel and 7 (19%) 2-vessel disease. After measurement of the transvalvular gradient over the aortic valve, cardiac output was determined by the thermodilution tech-

nique. Aortic valve orifice area was calculated by the Gorlin formula. The technique of aortic balloon valvuloplasty has been previously described in detail.[4]

Doppler echocardiography: All measurements were performed using a commercially available pulsed- and continuous-wave Doppler. Patients were examined 1 day before and <48 hours after balloon valvuloplasty, as well as at defined control intervals. To determine maximal velocities at the level of the aortic valve stenosis, standard views were obtained from the apical, right parasternal and suprasternal views. Mean and maximal instantaneous pressure gradients were calculated from the maximal and mean velocities measured in the left ventricular outflow tract and within the stenotic valve area, according to the modified Bernoulli equation. The diameter of the left ventricular outflow tract was measured from a parasternal long-axis view. The aortic orifice area was determined by the continuity equation whenever possible.[20] Calculation of the aortic valve orifice area during follow-up was performed by using the initial left ventricular outflow tract diameter. This was done to minimize the interobserver variability, which was previously shown to be 6%.[21] Doppler echocardiographic examinations were performed by well-trained and experienced physicians. Severity of the aortic insufficiency was estimated semiquantitatively by determining the amount of regurgitation in the left ventricle, using the apical and parasternal views. Regurgitation up to half of the left ventricle was classified as grade II, and up to two-thirds into the left ventricle as grade III. Aortic regurgitation of grade IV was determined if regurgitation was observed up to the left ventricular apex.

Follow-up: All patients were followed for a maximum of 18 months or until the patient underwent aortic valve replacement or died. The mean follow-up period was 10 ± 7 months (range 1 to 18). Patients were seen after 1, 3, 6, 12 and 18 months. Clinical status was assessed by patients' responses to a standard questionnaire. Clinical examinations and Doppler echocardiography were repeated according to a standard protocol.

Statistical evaluation: Clinical, hemodynamic and Doppler echocardiographic results are described as the mean value ± standard deviation. Changes of hemodynamic parameters were analyzed by a paired Student's *t* test.

RESULTS

Acute changes after percutaneous balloon valvuloplasty: INVASIVE QUANTIFICATION OF AORTIC VALVE STENOSIS BEFORE AND AFTER BALLOON VALVULOPLASTY: After balloon valvuloplasty, systolic peak gradient decreased from 78 ± 24 to 38 ± 13 mm Hg ($p < 0.001$). Aortic valve orifice area increased from 0.58 ± 0.23 to 0.93 ± 0.20 cm^2 ($p < 0.001$), whereas cardiac output remained unchanged in almost all patients. In 1 patient, aortic regurgitation of grade III was present after balloon valvuloplasty.

DOPPLER ECHOCARDIOGRAPHIC QUANTIFICATION OF AORTIC VALVE STENOSIS BEFORE AND AFTER BALLOON VALVULOPLASTY: The Doppler echocardiographic changes after balloon valvuloplasty are listed in Tables I through III. The maximal instantaneous gradient decreased from 96 ± 26 to 67 ± 22 mm Hg ($p < 0.001$). The aortic valve orifice area increased from 0.49 ± 0.16 to 0.73 ± 0.21 cm^2 ($p < 0.001$). Before valvuloplasty, aortic regurgitation was present in 22 patients (61%; grade I: 15 patients, grade II: 7 patients). After balloon valvuloplasty, aortic regurgitation developed or worsened in 12 patients (33%): in 5 patients each, grade 0 deteriorated to grade I/II or increased from grade I to II, and in 1 patient each, regurgitation deteriorated from grade II to III and from grade I to III.

Long-term results after percutaneous balloon valvuloplasty: CLINICAL OUTCOME AND DOPPLER ECHOCARDIOGRAPHIC RESULTS AFTER BALLOON VALVULOPLASTY: A total of 39 procedures of aortic balloon valvuloplasty were performed (including repeat valvuloplasty in 3 patients). Doppler echocardiographic data during the follow-up are listed in Tables I through III.

The in-hospital mortality rate after valvuloplasty was 8% (3 patients). In 1 patient, cardiopulmonary resuscitation was required during valvuloplasty because of ventricular fibrillation. This patient died from progressive cardiogenic shock 1 week after valvuloplasty. A second patient died immediately after valvuloplasty from cardiogenic shock, and a third patient died suddenly 3 hours after aortic valvuloplasty.

Thirty-three patients (92%) left the hospital and were followed for 10 ± 7 months (range 1 to 18). The life-table analysis revealed the time course during the follow-up (Figure 1). After 18 months, 17 patients (47%) were alive; however, only 9 patients were event-free and did not need further interventions. The change in aortic valve area and pressure gradient over the follow-up for the entire study population is shown in Figure 2. A continuous trend toward the preprocedural value was observed. Because of further analysis, patients were grouped as follows: patients who died during the follow-up period (group I), patients who underwent aortic valve replacement or repeated valvuloplasty (group II) and those who were either event-free or did not require further interventions (group III).

Fourteen patients (39%, group I) died after a mean of 6 ± 5 months (Table I). Doppler echocardiographic results obtained immediately after balloon valvuloplasty demonstrated a 62% increase in the aortic valve orifice area and a 33% decrease of the maximal instantaneous gradient. However, a clear tendency to restenosis could be observed after 1 month. After 6 months, the increase in the aortic valve orifice area was 19 ± 16% (Figure 3). When the last investigation before death was considered, aortic valve orifice area was calculated as 0.56 ± 0.1 cm^2 and the maximal instantaneous gradient as 78 ± 34 mm Hg; both values were similar to the preprocedural values.

Group II comprised 10 patients (28%) who underwent a second intervention (Table II). Seven patients (19%) underwent successful aortic valve replacement after a mean follow-up of 8 ± 7 months. In 1 patient, severe aortic regurgitation was observed after balloon valvuloplasty. Five patients required aortic valve replacement because of progressive heart failure. A repeat

valvuloplasty was performed in 3 patients (8%) because of clinical and hemodynamic evidence of restenosis. Two of these died from cardiogenic shock 1 week and 2 months after the second balloon valvuloplasty. Aortic valve replacement was performed after 6 months in the third patient. The Doppler echocardiographic results revealed that balloon valvuloplasty was less effective in these 10 (increase in aortic orifice area: 43 ± 22%). However, clinical symptoms initially improved in almost all patients. During follow-up, there was a slight deterioration of the aortic orifice area after 3 months in most patients. With regard to the last investigation before aortic valve replacement or before the second balloon valvuloplasty, aortic valve orifice area was similar to the preprocedural area in most of the patients, whereas the maximal instantaneous gradient remained lower than the prevalvuloplasty value.

In group III, 9 of 36 patients (25%) were alive and had an event-free course after balloon valvuloplasty. One patient refused the study after doing well for 18 months. In this group, 7 patients were clinically improved (NYHA class II). The other 2 patients, aged 83 and 74 years, were NYHA class III; both refused surgical intervention. Doppler echocardiographic measurements revealed a significant increase in the aortic valve area (47 ± 43%) and a significant reduction of the maximal instantaneous gradient immediately after balloon valvuloplasty (Table III). During follow-up, Doppler echocardiographic results revealed a slower deterioration of the initial success from valvuloplasty, compared with groups I and II (Figure 3).

DISCUSSION

Elderly patients with severe valvular aortic stenosis are known to be at increased risk for surgical intervention.[8] Consequently, there was increasing interest in the development and application of percutaneous balloon valvuloplasty as palliative treatment for severe aortic valve stenosis.[1–7] Several hemodynamic studies addressing the acute response of percutaneous balloon valvulo-

TABLE I Group I: Patients Who Died In-Hospital* and During Follow-Up (Aortic Valve Orifice Area [cm²]/Maximal Instantaneous Gradient [mm Hg])

Pt. No.	Balloon Valvuloplasty: Before	Balloon Valvuloplasty: After	Follow-Up: 1 Month	3 Months	6 Months	12 Months	18 Months
*	0.46/56	0.91/40					
*	—/102	—/74					
*	0.51/81	0.86/50					
1	0.51/151	0.60/117 (+18%/−23%)	0.60/118 (+18%/−23%)	0.60/120 (+18%/−21%)	0.56/125 (+10%/−17%)	0.50/161 (−2%/+7%)	+ SD
2	—/108	—/70 (—/−35%)	—/70 (—/−35%)	+ SD			
3	—/96	—/72 (—/−25%)	+ (unwitnessed)				
4	0.37/82	0.56/66 (+51%/−20%)	0.55/68 (+49%/−17%)	0.54/70 (+46%/−15%)	0.54/75 (+46%/−9%)	+ SD	
5	0.42/73	0.77/35 (+83%/−52%)	0.76/37 (+81%/−49%)	0.76/40 (+81%/−45%)	+ CHF		
6	—/98	—/80 (—/−18%)	+ SD				
7	0.50/75	0.78/32 (+56%/−57%)	0.60/81 (+20%/+8%)	0.57/85 (+14%/+13%)	0.57/85 (+14%/+13%)	+ CHF	
8	0.53/55	0.88/35 (+66%/−36%)	0.72/37 (+36%/−33%)	0.60/40 (+13%/−27%)	0.56/50 (+6%/−9%)	+ CHF	
9	0.60/59	0.70/49 (+17%/−17%)	+ CHF				
10	0.75/70	1.20/40 (+60%/−43%)	1.00/60 (+33%/−14%)	0.40/70 (−47%/0%)	+ CHF		
11	0.40/107	0.87/48 (+117%/−53%)	0.60/75 (+50%/−28%)	+ CHF			
12	0.40/94	0.60/65 (+50%/−31%)	+ CHF				
13	—/86	—/70 (—/−19%)	+ (unwitnessed)				
14	0.30/68	0.60/45 (+100%/−34%)	+ SD				
Mean values of the aortic valve orifice area							
	0.48 ± 0.12	0.76 ± 0.18 (+62 ± 30%)	0.69 ± 0.14 (+41 ± 20%)	0.57 ± 0.11 (+21 ± 39%)	0.56 ± 0.01 (+19 ± 16%)		
Mean values of the maximal instantaneous gradient							
	87.3 ± 23.9	58.9 ± 22.3 (−33 ± 13%)	68.3 ± 24.3 (−24 ± 16%)	70.8 ± 27.4 (−16 ± 19%)	83.8 ± 27.0 (−6 ± 11%)		

CHF = congestive heart failure; SD = sudden death; — = data not available.

TABLE II Group II: Patients Who Underwent Aortic Valve Replacement/Second Balloon Valvuloplasty (Aortic Valve Orifice Area [cm²]/Maximal Instantaneous Gradient [mm Hg])

Pt. No.	Balloon Valvuloplasty Before	Balloon Valvuloplasty After	Follow-Up 1 Month	Follow-Up 3 Months	Follow-Up 6 Months	Follow-Up 12 Months	Follow-Up 18 Months
1	0.57/115	0.69/74 (+21%/−36%)	0.72/57 (+26%/−50%)	0.75/63 (+32%/−45%)	0.65/78 (+14%/−32%)	AVR	
2	0.62/77	0.74/70 (+19%/−9%)	0.67/74 (+8%/−4%)	0.57/78 (−8%/+1%)	0.50/81 (−19%/+5%)	0.46/85 (−25%/+5%)	AVR
3	—/108	—/72 (—/−33%)	AVR				
4	—/100	—/60 (—/−40%)	—/60 (—/−40%)	—/72 (—/−28%)	AVR		
5	0.68/69	0.84/50 (+24%/−28%)	0.61/50 (−10%/−28%)	0.52/64 (−23%/−7%)	0.42/70 (−38%/+1%)	0.45/68 (−34%/−1%)	AVR
6	—/138	—/85 (—/−38%)	AVR				
7	0.35/140	0.60/105 (+71%/−25%)	0.60/105 (+71%/−25%)	AVR			
8	0.47/112	0.77/77 (+64%/−31%)	0.75/77 (+60%/−31%)	0.76/79 (+62%/−29%)	0.60/81 (+28%/−28%)	0.50/85 (+6%/−24%)	2.PBV + CHF
9	0.30/101	0.40/81 (+33%/−20%)	0.43/85 (+43%/−16%)	0.35/86 (+17%/−15%)	2.PBV + CHF		
10	0.30/130	0.50/109 (+67%/−16%)	0.52/100 (+73%/−23%)	0.47/105 (+57%/−19%)	0.42/109 (+40%/−16%)	0.40/116 (+33%/−11%)	2.PBV/AVR
Mean values of the aortic valve orifice area							
	0.47 ± 0.15	0.65 ± 0.14 (+43 ± 22%)	0.61 ± 0.1 (+39 ± 30%)	0.57 ± 0.15 (+23 ± 31%)	0.52 ± 0.09 (+5 ± 29%)	0.45 ± 0.04 (−5 ± 27%)	
Mean values of the maximum instantaneous gradient							
	109.0 ± 22.5	78.3 ± 17.2 (−28 ± 10%)	76.0 ± 18.7 (−27 ± 13%)	78.1 ± 13.4 (−19 ± 15%)	83.8 ± 13.2 (−14 ± 15%)	88.5 ± 17.3 (−8 ± 11%)	

AVR = aortic valve replacement; CHF = congestive heart failure; PBV = percutaneous balloon valvuloplasty; 2.PBV = second percutaneous balloon valvuloplasty.

TABLE III Group III: "Alive" Patients (Aortic Valve Orifice Area [cm²]/Maximal Instantaneous Gradient [mm Hg])

Pt. No.	Balloon Valvuloplasty Before	Balloon Valvuloplasty After	Follow-Up 1 Month	Follow-Up 3 Months	Follow-Up 6 Months	Follow-Up 12 Months	Follow-Up 18 Months
1	0.34/161	0.40/108 (+18%/−33%)	0.41/104 (+21%/−35%)	0.40/105 (+18%/−35%)	0.40/115 (+18%/−29%)	0.38/135 (+12%/−16%)	0.38/140 (+12%/−13%)
2	—/108	—/65 (—/−40%)					
3	0.51/120	0.70/63 (+37%/−48%)	0.62/79 (+22%/−34%)	0.50/101 (−2%/−15%)	0.52/107 (+2%/−11%)	0.43/115 (−16%/−4%)	0.40/121 (−22%/+1%)
4	0.67/99	0.87/88 (+30%/−11%)	0.82/84 (+22%/−15%)	0.78/81 (+16%/−18%)	0.75/82 (+16%/−18%)	0.71/83 (+12%/−17%)	0.71/83 (+6%/−16%)
5	0.47/94	0.49/68 (+4%/−28%)	0.50/64 (+6%/−32%)	0.51/67 (+9%/−29%)	0.53/70 (+13%/−26%)	0.57/68 (+21%/−28%)	0.53/68 (+13%/−28%)
6	0.44/102	0.50/85 (+14%/−17%)	0.50/85 (+14%/−17%)	0.50/90 (+14%/−12%)	0.45/95 (+2%/−7%)	0.45/92 (+2%/−10%)	0.45/95 (+2%/−7%)
7	0.30/70	0.65/51 (+117%/−27%)	0.65/50 (+117%/−29%)	0.62/58 (+107%/−17%)	0.60/60 (+100%/−14%)	0.60/60 (+100%/−14%)	0.55/68 (+83%/−3%)
8	0.36/68	0.80/32 (+122%/−53%)	0.60/40 (+67%/−41%)	0.58/48 (+61%/−29%)	0.55/56 (+53%/−18%)	0.46/67 (+28%/−1%)	0.51/67 (+42%/−1%)
9	1.00/93	1.35/70 (+35%/−25%)	1.29/77 (+29%/−17%)	1.10/88 (+10%/−5%)	1.00/104 (0%/+12%)	1.00/105 (0%/+13%)	0.90/116 (−10%/+25%)
Mean values of the aortic valve orifice area							
	0.51 ± 0.21	0.72 ± 0.28 (+47 ± 43%)	0.67 ± 0.26 (+37 ± 35%)	0.62 ± 0.21 (+31 ± 33%)	0.60 ± 0.18 (+26 ± 32%)	0.58 ± 0.19 (+20 ± 33%)	0.55 ± 0.16 (+16 ± 31%)
Mean values of the maximum instantaneous gradient							
	101.6 ± 26.2	70.0 ± 20.8 (−31 ± 13%)	72.9 ± 19.3 (−28 ± 9%)	79.7 ± 19.1 (−20 ± 9%)	86.0 ± 21.0 (−14 ± 12%)	90.5 ± 24.6 (−10 ± 12%)	94.8 ± 26.3 (−5 ± 14%)

plasty in severe aortic valve stenosis indicated a 50% reduction of the transvalvular pressure gradient and a 50 to 80% increase in the aortic valve orifice area. Most patients had marked improvement in clinical symptoms after balloon valvuloplasty. However, data concerning long-term results after aortic balloon valvuloplasty are disappointing. From several studies, a high mortality rate and a high incidence of restenosis ranging from 17 to 100% was evident during clinical follow-up.[7,10-19] These studies followed patients by clinical parameters. Invasive or Doppler echocardiographic measurements were performed only in a minority of patients in most studies, especially in patients in whom restenosis was clinically suspected.

Thus, this study was aimed at the consecutive evaluation of patients after balloon valvuloplasty by means of repeated Doppler echocardiographic measurements and of clinical follow-up concerning mortality, morbidity, clinical symptoms and the time course of restenosis. Like previous data, the Doppler echocardiographic results of the present study indicate that percutaneous balloon valvuloplasty resulted in significant hemodynamic and clinical improvement in the immediate post-procedural period.[18,22-24]

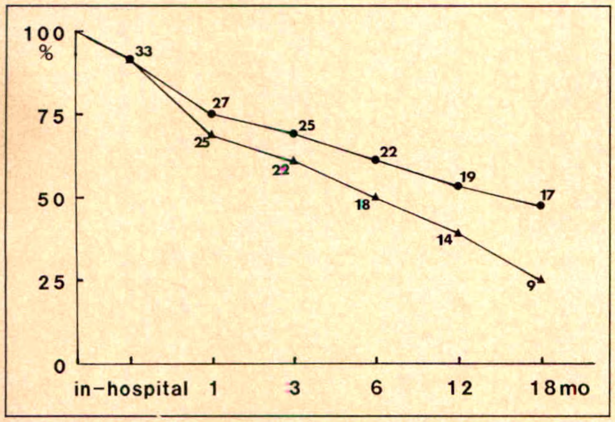

FIGURE 1. Mortality and secondary intervention rates during follow-up. *Circles* signify patients who died. *Triangles* signify patients who died and who had undergone aortic valve replacement or repeat balloon valvuloplasty.

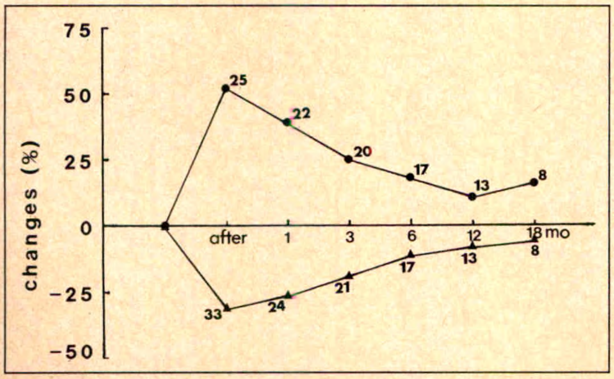

FIGURE 2. Mean percent changes in the aortic valve orifice area *(top portion)* and the maximal instantaneous gradient *(bottom portion)* determined by Doppler echocardiography in all patients after balloon valvuloplasty (after) and after 1, 3, 6, 12 and 18 months (mo).

The in-hospital mortality rate in our study amounted to 8%, which is comparable to the reported surgical risk of age-matched patients undergoing aortic valve replacement.[8] During a follow-up period of 10 ± 7 months, 44% of patients died. An additional 22% of patients required aortic valve replacement. Doppler echocardiographic measurements could demonstrate a continuous and significant increase of the transvalvular aortic gradient and a decrease of the aortic orifice area during the follow-up period in all patients. However, compared with long-term survivors after balloon valvuloplasty (group III), patients who died (group I) or underwent aortic valve replacement or a second valvuloplasty (group II) were more likely to have an early increase of the transvalvular gradient and a decrease in

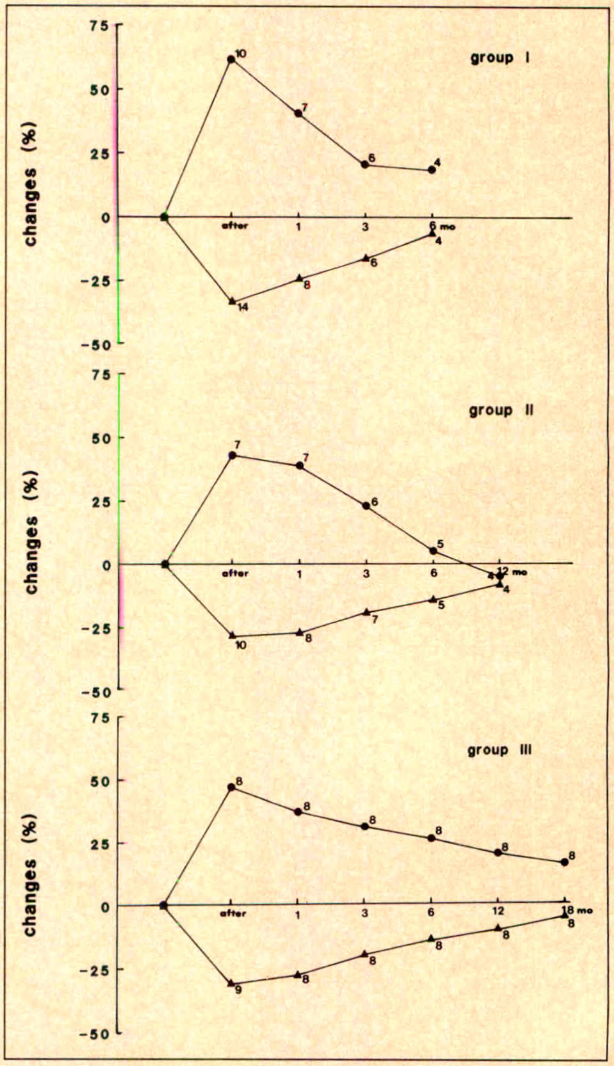

FIGURE 3. Mean percent changes in the aortic valve orifice area *(top portion* of each graph) and the maximal instantaneous gradient *(bottom portion* of each graph) determined by Doppler echocardiography after balloon valvuloplasty (after) and during a follow-up of 1, 3, 6, 12 and 18 months (mo). Group I are patients who died during follow-up, group II are patients who required an aortic valve replacement or a second percutaneous balloon valvuloplasty, and group III are patients who were either event-free or did not require further interventions during follow-up.

the aortic orifice area (Figure 3). The initial success of valvuloplasty with regard to the aortic valve orifice area was smallest in the group of patients who required aortic valve replacement or a second valvuloplasty. Interestingly, clinical symptoms were initially improved. This can best be explained by the fact that minimal changes in the aortic valve orifice area are sufficient to achieve clinical improvement, as long as the so-called "critical" level of restenosis is not yet reached.[25] On the other hand, clinical improvement can also be due to a placebo effect, as well as to advanced modalities of medical treatment.

Doppler echocardiography is an accepted noninvasive technique for the quantification of the severity of aortic valve stenosis.[20,26–30] Several studies have demonstrated a close relation between catheterization and Doppler-derived data for aortic valve orifice area and for mean pressure gradients. The accuracy of hemodynamic data measured by experienced laboratories allows judgment of the relatively small hemodynamic changes. Additionally, this method allows frequent measurements and is therefore particularly useful in controlling the clinical course. In the present study, the Doppler echocardiographic results demonstrated immediate improvement of the hemodynamic data in the postprocedural period. During the follow-up period, progressive deterioration of the valvuloplasty success was observed in most of the patients. The Doppler echocardiographic changes were relatively small; however, a continuous trend toward the preprocedural severity of the aortic valve stenosis was present.

In summary, death or restenosis occurred in the majority of patients undergoing percutaneous balloon valvuloplasty after a follow-up period of 18 months. Doppler echocardiographic measurements clearly demonstrate the progression of restenosis in most of the patients. These results warrant reconsideration of the indication of percutaneous balloon valvuloplasty for patients with severe aortic valve stenosis.

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Effect of Heart Rate on Left Ventricular Diastolic Transmitral Flow Velocity Patterns Assessed by Doppler Echocardiography in Normal Subjects

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Although a number of factors, including age and ventricular loading, are known to influence the pattern of left ventricular (LV) filling as depicted by Doppler echocardiographic transmitral flow velocities, few and conflicting data are available regarding the influence of heart rate (HR). Therefore, 20 volunteers (mean age 30 years) were evaluated with pulsed-wave Doppler echocardiography, performed with the sample volume placed at the mitral anulus level in the apical 4-chamber projection. Transmitral flow measurements comprised peak and integrated early passive (E) and late atrial (A) filling velocities and the slope of velocity decline from peak E filling. Measurements were recorded during baseline (sinus rhythm, mean 70 beats/min) and during transesophageal atrial pacing (mean 88 beats/min). LV end-diastolic dimension, mean arterial pressure and PR interval (corrected for pacing-induced delay in interatrial conduction time) were unchanged during pacing versus baseline measurements. Peak and integrated E filling velocities averaged 0.59 ± 0.09 m/s and 6 ± 1 cm, respectively, at baseline and were not significantly greater at the higher HR. In contrast, baseline peak and integrated A velocities averaged 0.37 ± 0.06 m/s and 2.3 ± 0.7 cm, respectively, but were significantly greater at the higher HR (0.5 ± 0.07 m/s and 3.2 ± 1.1 cm, respectively [p <0.003 vs baseline for each]). Further analysis of a subgroup of 9 subjects for whom Doppler measurements were available at 3 HRs (sinus 70; pacing 80 and 90) yielded strong evidence for a linear relation between HR and peak A velocity (A = 0.008 HR − 0.21, with p <0.0001 for significance of the linear trend). It is concluded that (1) HR influences Doppler patterns of diastolic filling, (2) as HR increases, E velocity is unchanged but A velocities increase, and (3) for each increase of 10 beats/min in HR, peak A velocity can be expected to increase by 8 cm/s.

(Am J Cardiol 1991;67:622–627)

From the Division of Cardiology, College of Medicine, University of Kentucky, Lexington, Kentucky. Manuscript received September 26, 1990; revised manuscript received and accepted November 2, 1990.

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The pattern of left ventricular (LV) filling as depicted by Doppler echocardiographic transmitral flow velocities has been used to assess LV diastolic properties. The use of Doppler echocardiography for this purpose is limited, however, because a number of variables may influence transmitral flow patterns, including age,[1] preload,[2–4] afterload[5] and systolic function.[6] Although heart rate (HR) has been implicated as an additional variable capable of influencing the LV filling pattern, data regarding this relation are sparse and conflicting.[7–12] The potential influence of HR is particularly important, because changes in serial Doppler examinations secondary to concomitant changes in HR could be attributed to alterations in LV diastolic behavior. Therefore, we systematically studied the effect of changes in HR produced by transesophageal atrial pacing on Doppler measurements of transmitral flow in 20 normal subjects. The studies were performed with the following objectives: (1) to establish the ability of changes in HR to alter Doppler parameters of LV diastolic filling, (2) to determine the nature of alterations in individual Doppler measurements imparted by changes in HR, and (3) to provide a way to estimate the magnitude of the effect of altered HR on various Doppler measurements.

METHODS

Study group: Twenty healthy volunteers (19 men, 1 woman) aged 24 to 42 years (mean 30) comprised the study group. All subjects were determined to be free of any acute or chronic illness by history, physical examination, electrocardiogram and 2-dimensional echocardiogram. The study was approved by the institutional review board of the University of Kentucky, and informed, written consent was obtained before the protocol began. Subjects were fasting, and were neither sedated nor receiving any medication at the time of the study.

Transesophageal atrial pacing: Subjects were prepared by nasal administration of a small amount of a 50:50 mixture of 4% lidocaine and 0.1% phenylephrine. A 7Fr bipolar pacing catheter was then passed through the nares and into the esophagus.[13] Final positioning of the pacing electrode was accomplished by electrocardiographic monitoring until consistent, continuous atrial capture was achieved (Figure 1). Stable atrial capture usually required 10-ms pulses of 15 to 25 mA in intensity, which was provided by the pacing device (Stat-Pace

II, Secor Inc.). Although the pacing device is quite reliable, the calibration scale on the model used in this study did not allow for absolutely precise MR manipulation. Thus, the HRs reported are derived from the RR intervals of the cardiac cycles for which Doppler profiles were analyzed.

Doppler studies: With the transesophageal pacing electrode in place and the subject in the supine position with a left lateral tilt, pulsed-wave Doppler ultrasound examination was performed. Studies were obtained at rest and at pacing rates of 10 and 20 beats/min higher than the spontaneous HR to an upper limit of 90 beats/min, beyond which useful Doppler tracings were no longer available (see later). The Doppler examination was obtained with commercially available equipment with a 2.5-MHz transducer. During imaging in the apical 4-chamber view, the sample volume was placed at the level of the mitral anulus and transducer orientation, instrument gain settings and sample volume location were adjusted in order to obtain the highest velocity of discrete Doppler signals. Optimal orientation of the Doppler beam was judged to have been attained when maximal peak flow velocities with a narrow spectrum were reproducibly obtained, as evidenced by both audio and spectral displays. The angle between the interrogating beam and the apparent direction of blood flow was judged to be <20° in all instances, and no correction factor was used. Care was taken to insure that the sample volume position remained constant for examinations at each HR. Hard copy recordings of ≥20 cardiac cycles were obtained at a paper speed of 50 to 100 mm/s for subsequent analysis and measurement. Subjects maintained a comfortable shallow respiratory pattern throughout the protocol.

Off-line quantitation of the Doppler recordings was performed with a computer-integrated digitizing pad (Nova Microsonics, Indianapolis) and specifically designed software (Freeland Medical Systems). Flow profiles for 3 consecutive representative cardiac cycles were analyzed by tracing the darkest portions (modal velocity) of the spectral printout and averaging the values. Because of fusion of early passive (E) and late atrial (A) velocities at high HRs, a perpendicular was drawn to the baseline from the point of onset of increasing velocities attributable to atrial contraction in order to enable separation of E and A velocities at these higher rates. Peak velocities of E and A filling periods, as well as integrated velocities for total E and A filling, were measured. Tracing of integrated velocities at slower HRs was performed by extension of the diagonals to the baseline from the upsloping and downsloping portions of E and A filling profiles. Thus, the small amount of flow occurring during the relative diastasis of mid-diastole was not included in the tracing of these integrated velocities. When the percentage of total flow velocity integral contributed by A was evaluated, however, total flow velocity integral included flow occurring in mid-diastole (diastasis). The slope of the velocity decline from peak E filling velocity (E-F) was measured as the rate of decline in velocity from peak E velocity to baseline. If rapid HR resulted in onset of A filling velocity before the conclusion of E filling velocity, the declining slope of the E filling velocity profile was extrapolated to the baseline from the point of onset of A velocity.

Blood pressure was measured by cuff sphygmomanometer, and 2-dimensional echocardiography was performed from parasternal and apical windows. LV dimensions were measured from hard copy recordings of 2-dimensional-directed M-mode echocardiograms recorded from the parasternal window at each HR, with care taken to maintain the same cursor position within the left ventricle. The values reported are averages of measurements derived from 3 consecutive representative cardiac cycles.

Statistical analysis: Data are reported as mean values ± 1 standard deviation. Probability values refer to the results of Student's t test for paired data when Doppler values obtained at different HRs are compared. For analysis of the subpopulation with 3 different HRs, the data were subjected to an analysis of variance for a single-group repeated measures design. A contrast was constructed to test for the significance of a linear trend among the mean responses as part of this analysis of variance.[14]

RESULTS

The pacing electrode was placed without difficulty and yielded consistent atrial capture in all subjects. Although minor discomfort caused by pacing was occasionally experienced, it was easily tolerated. All subjects maintained 1:1 atrioventricular conduction during pacing. Because of fusion of E and A velocity profiles at rapid rates, the highest pacing frequency at which E and A velocities could be reliably distinguished was approximately 90 beats/min. Thus, although all subjects were successfully paced to a HR 10 beats greater than that at rest, only 12 subjects could be paced at 20

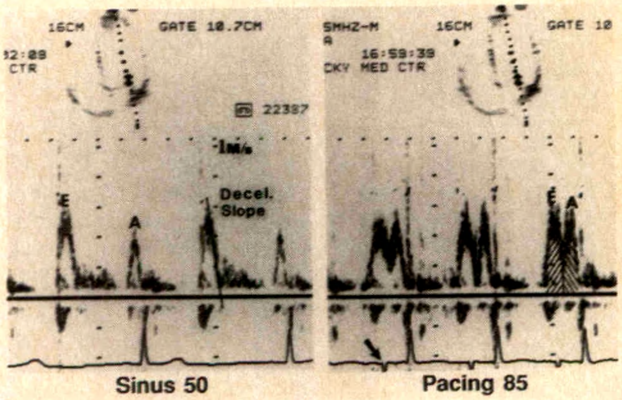

FIGURE 1. Pulsed-wave Doppler velocity profile from the apical 4-chamber view with the sample volume at the level of the mitral anulus. At the spontaneous heart rate of 50 beats/min, peak E velocity is approximately 0.55 m/s, whereas peak A velocity is approximately 0.4 m/s. During atrial pacing at 85 beats/min, peak E velocity is minimally changed, but peak A velocity has increased to nearly 0.6 m/s. Pacing artifact is indicated by the *arrow*. Deceleration (Decel.) slope from peak E velocity is indicated by the *solid dark line*. *Cross-hatched areas* indicate integrated velocities for early and atrial portions of diastole. A = late atrial filling velocity; E = early passive filling velocity.

TABLE I Physiologic Changes with Pacing

	Baseline	Pacing	p Value
Heart rate (beats/min)	70 ± 10	88 ± 3	0.0001
Mean arterial pressure (mm Hg)	88 ± 8	91 ± 9	NS
LV end-diastolic dimension (cm)	5 ± 0.5	5 ± 0.4	NS
Corrected PR (ms)	160 ± 15	161 ± 235	NS

LV = left ventricular; NS = not significant.

beats/min above baseline and still maintain distinct E and A waves.

Physiologic changes during pacing (Table I): Before pacing, baseline HR averaged 70 ± 10 beats/min, mean arterial pressure averaged 88 ± 8 mm Hg, LV end-diastolic dimension averaged 5.2 ± 0.5 cm, and the PR interval averaged 160 ± 15 ms. Pacing at the highest HR resulted in an increase of 18 to 88 ± 3 beats/min ($p < 0.0001$). Neither mean arterial pressure nor LV end-diastolic dimension was significantly altered by pacing. The PR interval during pacing was artificially lengthened to 191 ± 22 ms because of the time required for interatrial conduction. The increase in interatrial conduction due to atrial pacing has been shown to be constant, between 25 and 30 ms, over a wide range of pacing rates and averages.[15] When the PR interval was corrected by subtracting 30 ms, pacing did not result in a significant alteration in the PR interval from baseline.

Doppler results during sinus rhythm and pacing (Table II, Figures 2 through 4): At baseline, peak E velocity averaged 0.59 ± 0.09 m/s. At the highest pacing rate (88 beats/min), peak E velocity averaged 0.61 ± 0.14 m/s, which was not significantly different from baseline. Peak A velocity at baseline averaged 0.37 ± 0.06 m/s. During pacing at the highest HR, peak A velocity averaged 0.5 ± 0.07 m/s, which was substantially increased from baseline ($p < 0.0001$). The ratio of E to A peak velocities, which had averaged 1.63 ± 0.39 at baseline, decreased during pacing to 1.24 ± 0.23 ($p < 0.0001$).

At baseline, integrated E velocity averaged 6 ± 1 cm. At the highest pacing rate, integrated E velocity averaged 6.1 ± 1.8, which was not significantly different from baseline. Integrated A velocity averaged 2.3 ± 0.7 cm at baseline and significantly increased during pacing at the highest rate to an average value of 3.2 ± 0.8 ($p < 0.003$). Although the sum of integrated E and A velocities was greater at the higher HR, this should not be interpreted as an increase in total stroke volume with pacing, because velocities during the relative "diastasis" of mid-diastole at lower HRs were not included (see Methods). The ratio of E and A integrated velocities, which had averaged 2.87 ± 1.08 at baseline, decreased during pacing to 2.03 ± 0.64 ($p < 0.01$). The percentage of flow velocity integral supplied by A averaged 27 ± 6% at baseline and increased to 36 ± 13% by pacing at the highest HR ($p < 0.003$).

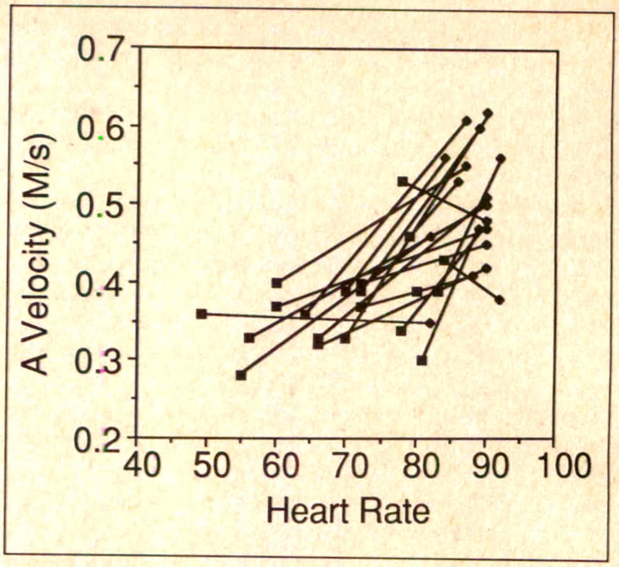

FIGURE 2. Effect of heart rate on peak A velocity. Peak A velocity consistently increases as heart rate is elevated from baseline heart rate *(squares)* to the higher pacing rate *(diamonds)*. Abbreviation as in Figure 1.

At baseline, E-F averaged 5.02 ± 1.2 m/s². At the highest pacing rate, this slope diminished slightly, to 4.34 ± 1.2 m/s² ($p < 0.03$).

Predicting Doppler values at differing heart rates (Figure 4): To better define the relation between peak A filling velocity and HR, a subpopulation of 9 subjects who had spontaneous HRs approximating 70 beats/min (mean 68) were paced at HRs of both 80 and 90 beats/min. For this subgroup, Doppler values for peak A velocity during sinus rhythm averaged 0.36 ± 0.03 m/s. Peak A velocity at 80 beats/min averaged 0.44 ± 0.09 m/s and peak A velocity at 90 beats/min averaged 0.52

TABLE II Mean ± Standard Deviation (Range) for Doppler Measurements at Baseline and During Pacing at the Highest Heart Rate

	Baseline	Pacing	p Value
Peak E (m/s)	0.59 ± 0.09 (0.43–0.74)	0.61 ± 0.14 (0.36–0.94)	NS
Peak A (m/s)	0.37 ± 0.06 (0.28–0.53)	0.50 ± 0.07 (0.35–0.62)	0.0001
E_{FVI} (cm)	6 ± 1 (3.7–7.9)	6.1 ± 1.8 (2.2–9.3)	NS
A_{FVI} (cm)	2.3 ± 0.7 (0.9–4)	3.2 ± 0.8 (1.8–4.8)	0.0026
Peak E/A	1.63 ± 0.39 (1.1–2.5)	1.24 ± 0.23 (0.81–1.6)	0.001
E/A FVI	2.87 ± 1.08 (1.67–5.89)	2.03 ± 0.64 (0.61–3)	0.012
$\%A_{FVI}$	27 ± 6 (13–37)	36 ± 13 (20–83)	0.003
E–F slope (m/s²)	5.02 ± 1.2 (2.64–7.59)	4.34 ± 1.2 (2.26–6.04)	0.03

A = atrial filling velocity; E = early filling velocity; E-F = slope of deceleration from peak early filling; FVI = flow velocity integral; NS = not significant; $\%A_{FVI}$ = percentage of total flow velocity integral contributed by atrial contraction.

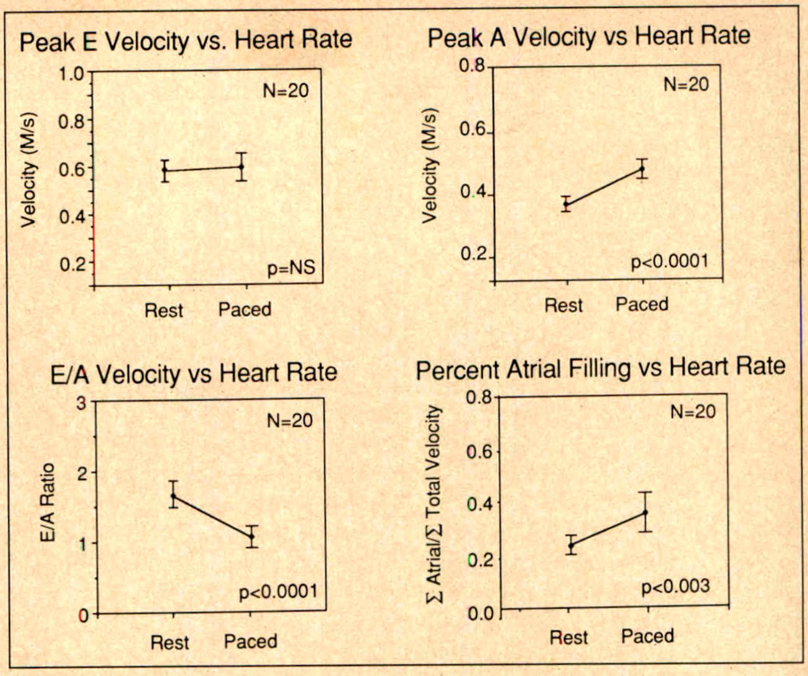

FIGURE 3. Summary of the changes in Doppler measurements due to alteration in heart rate. Values displayed are average velocity values at baseline heart rate and the higher pacing heart rate. P values were derived by Student's *t* test for paired data. Σ = integrated velocity; NS = not significant; other abbreviations as in Figure 1.

± 0.08 m/s. When these values underwent regression analysis with HR, a linear relation was observed, which was described by the equation: $A = 0.008\ HR - 0.21$, with $p < 0.0001$ for significance of the linear trend. Thus, for each increase of 10 beats/min in HR, peak A velocity increased by 8 cm/s.

DISCUSSION

Doppler echocardiographic measurement of transmitral flow velocity has been used by many investigators in attempts to assess LV diastolic performance.[16-20] Although Doppler velocity profiles have been shown to correspond well to volumetric filling of the left ventricle,[21,22] it is clear that multiple factors can influence E and A velocities.[1-6] Few data exist, however, regarding the influence of HR on Doppler values of diastolic flow velocity. The present study provides clear evidence that modification of HR alters diastolic velocity profiles and indicates that such changes should be considered when using Doppler echocardiography to assess diastolic properties. Furthermore, these data establish that the relation between HR and peak A velocity is linear in young normal subjects over the range of HR studied, and thereby provide a basis by which to correct peak A velocity for HR.

Relation of heart rate to transmitral flow velocities: In a population-based study of Doppler velocities in 215 healthy subjects between 1 and 65 years of age, Van Dam et al[10] found a significant relation between HR and E/A velocity that they considered relevant only in younger subjects with a lower HR. Similarly, Smith et al[11] found that the stimulation of a cold pressor test, an intervention that induced an increased HR, was associated with significant alterations in E/A, principally due to an increase in A velocity. Preliminary abstracts[7-9] have also proposed a relation between HR and Doppler patterns of mitral inflow.

The present study is the first to analyze the relation between HR and transmitral Doppler flow profiles systematically. Even a modest change in HR altered peak and integrated A filling velocity. Interestingly, previous experimental data[23] obtained by measuring transmitral flow volume at the mitral anulus with electromagnetic flow probes showed E filling volumes to remain unchanged, while A filling volume increased as HR was elevated.

Potential explanations for the heart rate–Doppler velocity relation: Several possible explanations exist to explain the interaction between HR and Doppler velocities. First, an increase in HR might lead to impaired LV relaxation, with reversal of predominant filling from

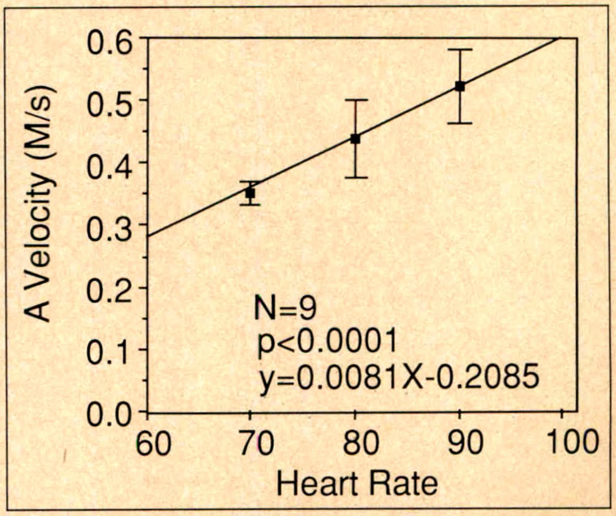

FIGURE 4. Predictability of the effect of heart rate on peak A velocity for 9 subjects for whom Doppler values were available at 3 different heart rates. P value refers to analysis of variance for repeated measures (see text). Abbreviation as in Figure 1.

early-to-late diastole. However, our data failed to show either a decrease in peak E velocity or a major diminution (or flattening) of E-F, 2 characteristics known to be typical of abnormal relaxation.[24] Thus, it appears unlikely that abnormal relaxation played a role in altering the filling pattern in these young normal subjects. Second, the loss of diastolic filling time as HR increases may result in incomplete left atrial emptying before the onset of the atrial contraction. Therefore, a greater left atrial volume may be present at the time of atrial systole, enabling a large flow volume for a given atrial contraction. The greater atrial volume actually may enhance atrial performance in a fashion similar to that of the Frank-Starling mechanism, resulting in a larger flow volume because of atrial systole. In addition, the volume entering the left ventricle during prolonged mid-diastolic diastasis at slow HRs will be delivered during atrial systole at higher HRs. Third, at a higher HR, the left ventricle may be relatively empty and at a low point on its diastolic pressure-volume curve at the time of atrial contraction. Given the curvilinear shape of the left ventricle's diastolic pressure-volume relation,[25,26] an underfilled left ventricle would be more compliant and better able to accept the volume delivered by atrial contraction. Finally, the "force-frequency" relation of Bowditch[27,28] could apply to the left atrium as well as to the left ventricle, resulting in greater left atrial contractility at a higher HR. Although any of the latter 3 mechanisms might be valid, it should be emphasized that they are not mutually exclusive and are likely to function in concert.

Study limitations: Increases in HR due to pacing are known to result in a linear decline in LV end-diastolic dimension.[29,30] Because changes in preload are known to influence transmitral Doppler flow profiles, our results could have been influenced by changing preload. We altered HR by an average of only 18 beats/min, however, and carefully performed echocardiographic studies have revealed minimal alteration in LV dimension over this range. Previous work[30] has shown that the decrease in LV dimension as HR is increased from 70 to 90 beats/min is approximately 2.5 mm. In the present study, the decrease in LV dimension that occurred with pacing did not reach statistical significance. Thus, any change in LV dimension that may have occurred in this study was small enough to escape detection, whereas alterations in Doppler velocities were quite obvious.

We measured transmitral Doppler velocities at the level of the mitral anulus. Velocities at this position are clearly different from Doppler velocities obtained at the tips of the mitral leaflets.[31] We chose the sampling position to optimize reproducibility of sample volume placement from 1 pacing HR to the next and because the cross-sectional area at the level of the anulus is less variable throughout diastole than at the tips of the mitral leaflets. Moreover, although absolute values for E and A velocities are different when measured at the leaflet tips versus at the anulus, the directional change in these velocities produced by an intervention is likely to be similar.

The discomfort associated with transesophageal pacing may have altered loading conditions by stimulating sympathetic or parasympathetic responses. However, we found no significant increase or decrease in mean arterial pressure or symptoms to suggest an adverse response to pacing. Finally, although it has been demonstrated that alteration of the PR interval can influence diastolic filling pattern,[32] the PR was unchanged in our subjects despite pacing once interatrial conduction time was considered.[15]

Clinical implications: Enthusiasm for the application of transmitral Doppler velocities to the evaluation of diastolic performance has tempered recently because of reports describing the influence of age and hemodynamic variables on the velocity profile. This study serves to confirm earlier reports regarding the influence of HR on Doppler parameters of diastolic function. Future clinical and experimental use of these measurements must consider HR as another potentially confounding factor.

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Effects of the Immunosuppressant Cyclosporine on the Circulation of Heart Transplant Recipients

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The effect of cyclosporine on the systemic circulation and on heart rate is unknown for heart transplant recipients. Thirty-four heart transplant recipients were studied by right-sided cardiac catheterization after endomyocardial biopsy. A direct linear relation was found between systemic and pulmonary vascular resistance and cyclosporine trough blood levels, which were negatively related to heart rate. The effect of cyclosporine on pulmonary vascular resistance, however, was not statistically significant by multivariate analysis when patient age was considered. In contrast, renal function appeared unrelated to systemic vascular resistance or heart rate. It appears that cyclosporine trough blood levels may have a direct effect on systemic vascular resistance as well as an unexplained negative chronotropic effect on heart rate.

(Am J Cardiol 1991;67:628–632)

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Immunosuppressant treatment with cyclosporine is not without complications. Renal impairment[1] and hypertension[2] are the most frequent and troublesome adverse effects. Hypertension, thought to result from a vasopressor effect of cyclosporine,[3] occurs after both acute intravenous and short-term oral treatment,[4–6] and is most marked with intravenous administration, causing severe reduction of blood flow to many organs, including lungs.[7] The associated systemic hypertension does not appear to be related to the degree of renal dysfunction, as it is associated with both normal and even low plasma renin activity in humans.[8]

The increase in systemic vascular resistance may be the result of a variety of factors. Local elevation in sympathetic tone,[9,10] diminished or blocked prostacyclin production,[11,12] attenuation of nitrate-based vasorelaxation[13] and intact innervation[14] appear to be the most important.

To determine whether cyclosporine trough levels had any influence on vascular resistance as well as on heart rate at rest, we measured pulmonary and systemic vascular resistance at rest and after vasodilatation in patients who had undergone heart transplantation, and who were receiving maintenance immunosuppression with cyclosporine and azathioprine, often in conjunction with low-dose steroids.

METHODS

A total of 34 patients who underwent heart transplantation (33 men and 1 woman, mean age 37 years [range 20 to 61]) were prospectively studied at the time of routine endomyocardial biopsy, between 2 and 18 months (mean 7) after surgery. No patient had cardiac rejection at the time of study. Seven were receiving oral nifedipine for systemic hypertension and 2 were receiving oral captopril.

Lung disease likely to be associated with hypoxia was excluded by history, examination and measurement of lung volumes (Gould 2800 Autobox, Dayton, Ohio), by single breath gas transfer factor for carbon monoxide (PK Morgan, Chatham, Kent, England) and by spirometry.

Serum urea, creatinine, electrolyte and blood hemoglobin levels were determined on the day of the study. Trough cyclosporine levels were measured immediately before the study for blood and plasma by a nonspecific radioimmunoassay capable of detecting parent drug and metabolites[15] and by a new and specific monoclonal ra-

dioimmunoassay for the parent drug.[16] Patients did not receive cyclosporine until the study was completed.

After standard endomyocardial biopsies, a flow-directed pulmonary artery catheter (either a 7Fr Gould model SP5107, or a 7Fr Edwards model 93A-131, Edwards Laboratories, Anasco, Puerto Rico) was inserted, using a right internal jugular approach. Mean pulmonary wedge, right atrial and pulmonary artery pressures were recorded with digital readout monitors (Datascope Acucep, PK Morgan). Cardiac output was measured by the thermodilution technique (either Gould Strathan SP1435 Cardiac Index Computer, Mitchum, England, or Edwards 9025A Cardiac Computer, Edwards Labs). Measurements were taken at rest and every 10 minutes by the same physician as prostacyclin was infused at 2, 4 and 6 ng/kg/min via a side arm into the right internal jugular vein. Prostacyclin was then stopped and baseline measurements taken 10 minutes later. Nitric oxide (30 ± 2 ppm) in air was inhaled for 3 minutes before or after prostacyclin infusion, the order chosen at random, with a 10-minute lapse between administration of each agent. The nitric oxide inhalation was compared with an inhalation of air, both administered blindly every 3 minutes, with air from Douglas bags. Results were then averaged. Nitric oxide concentrations were measured immediately before and after the study by a chemiluminescent analyzer (G.R. and D.C., Southampton, England). Hemodynamic measurements were taken in the last minute of each 3-minute interval.

Systemic blood pressure was measured by auscultation with a manometer on the left arm at the time of all other readings.

Statistical analysis: Results are reported as mean ± standard deviation. A p value <0.05 was considered statistically significant, although values ≤ 0.1 are also reported.

Cardiac output, heart rate, and systemic and pulmonary vascular resistance were assessed as outcome measures reflecting hypertension. Renal dysfunction was measured in terms of creatinine clearance and serum creatinine.

To assess the relations among cyclosporine, hypertensive and renal outcome measures, a series of linear regression analyses were performed, with cyclosporine the independent variable and outcome the dependent variable. Because it is not clear which measurement of cyclosporine is the most useful predictor of outcome, trough blood, plasma and serum cyclosporine levels were used.

Changes in hemodynamic measurements before and after infusion of 6 ng/kg/min of prostacyclin were assessed using paired Student *t* tests. Similarly, paired Student *t* tests were used to test the hemodynamic differences between inhaling air and nitric oxide.

RESULTS

Time after surgery ranged from 2 to 18 months. Blood chemistry samples were taken immediately before the study, as were trough levels for cyclosporine. Twenty-four hour urine samples were taken over the preceding 24 hours. Significant linear regression analyses are given for systemic and pulmonary vascular resistance, cardiac index and heart rate at rest (Figures 1 through 5).

Regression analysis failed to show any correlation zbetween any vascular resistance (Table I) and either serum creatinine or creatinine clearance. In contrast, both pulmonary and systemic vascular resistance were significantly correlated with trough levels of all 3 cyclosporine measurements.

The only significant determinant of systemic vascular resistance by multiple regression analysis of all independent factors, including the dose of oral vasodilators, was cyclosporine trough levels by all 3 assays. This was unchanged with multiple regression analysis using the variables listed in Table I.

Together with preoperative pulmonary vascular resistance and patient age, pulmonary vascular resistance

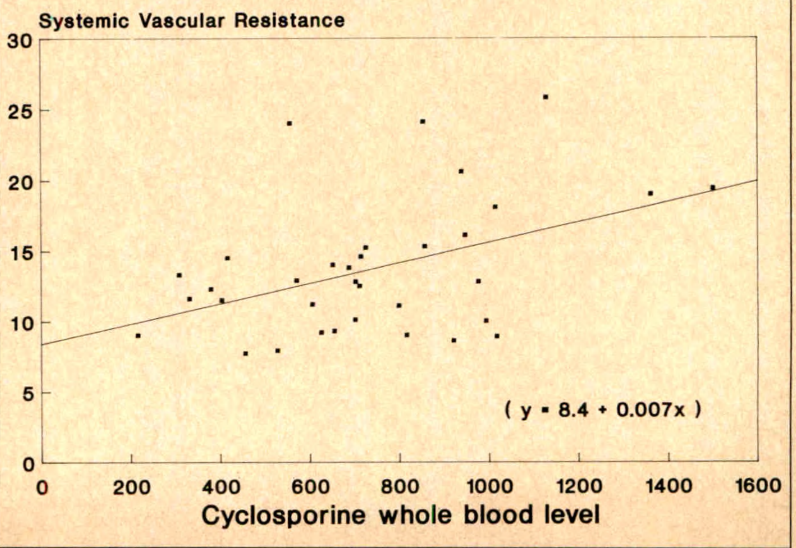

FIGURE 1. Baseline systemic vascular resistance in Wood units (mm Hg · min/liter) plotted against whole blood cyclosporine levels in ng/ml by the nonspecific radioimmunoassay.[15] The *linear regression line* is given, with p = 0.010 (F = 7.49; 1,32).

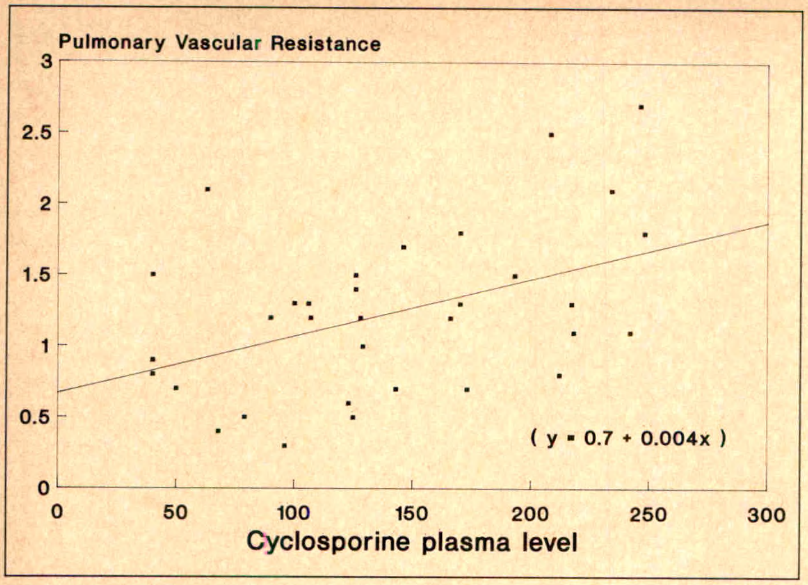

FIGURE 2. Baseline pulmonary vascular resistance in Wood units (mm Hg · min/liter) plotted against plasma cyclosporine levels in ng/ml by the nonspecific radioimmunoassay.[15] The *linear regression line* between the 2 variables is given, with p = 0.0066 (F = 8.44; 1,32).

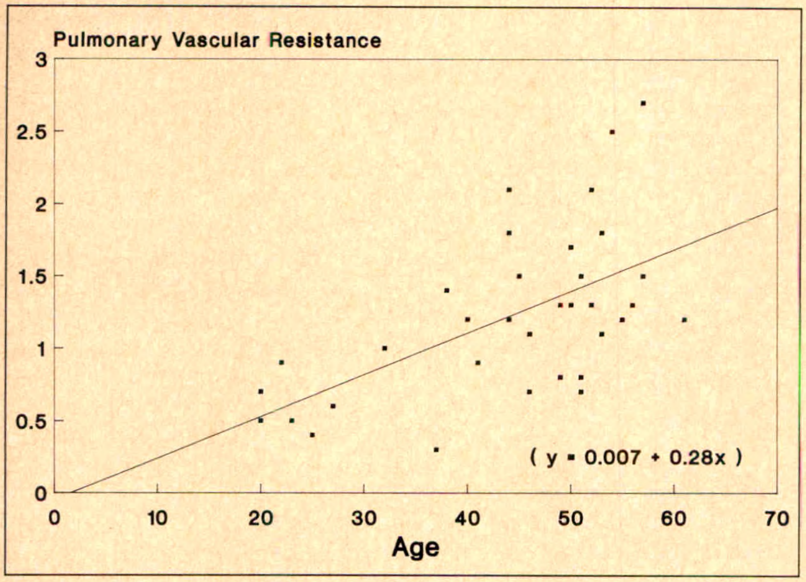

FIGURE 3. Baseline pulmonary vascular resistance in Wood units (mm Hg · min/liter) plotted against age in years. The *linear regression line* between the 2 variables is given, with p = 0.0004 (F = 15.59; 1,32).

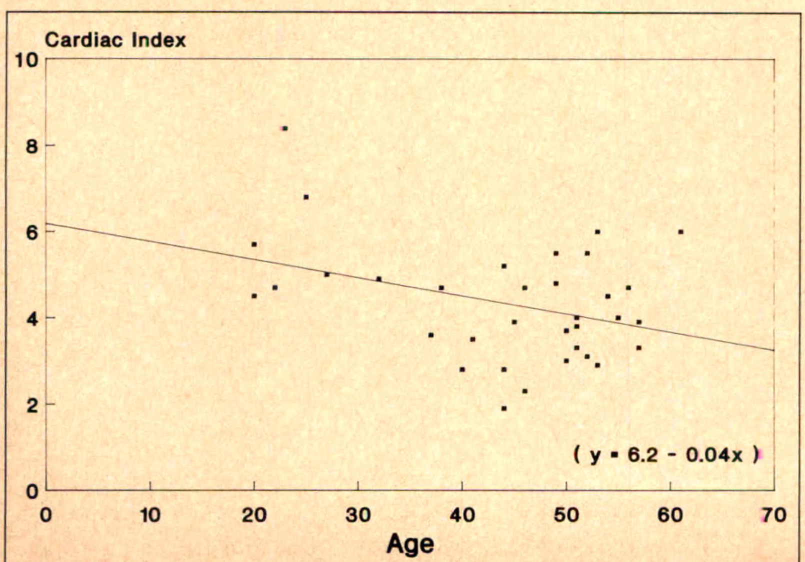

FIGURE 4. Baseline cardiac index in liters/min/m^2 plotted against age in years. The *linear regression line* between the 2 variables is shown, with p = 0.0329 (F = 4.97; 1,32).

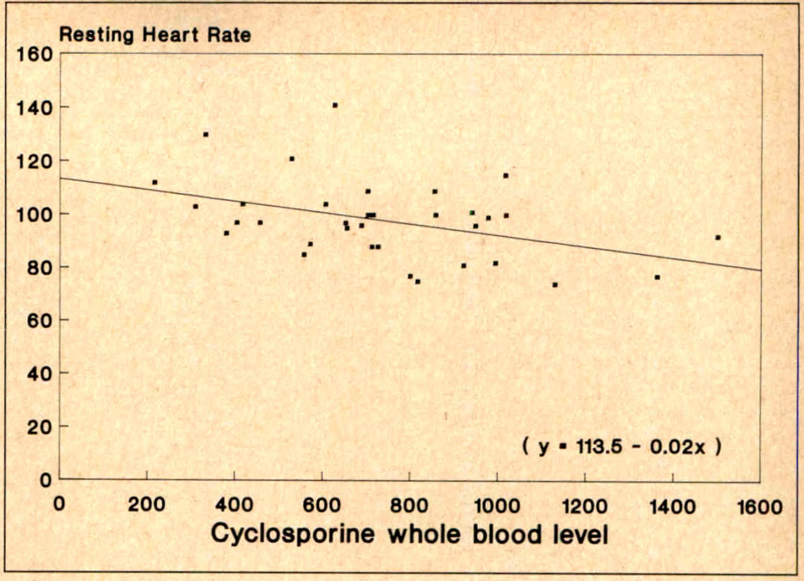

FIGURE 5. Baseline heart rate in beats per minute plotted against whole blood cyclosporine levels measured in ng/ml by the nonspecific radioimmunoassay.[15] The *linear regression line* between the 2 variables is given, with p = 0.01566 (F = 6.516; 1,32).

correlated with trough cyclosporine levels by all 3 assays. However, multivariate analysis suggests that age is the major determinant of pulmonary vascular resistance. Heart rate at supine rest was negatively related to cyclosporine trough levels and, to a lesser extent, negatively related to the age of the patient, but not the age of the donor. Multivariate analysis suggests that cyclosporine trough level is the major determinant of heart rate at supine rest.

Prostacyclin was associated with a decrease in systemic vascular resistance ($p < 0.001$), with a slight increase in heart rate ($p < 0.001$), and an increase in cardiac index ($p < 0.001$). The inhalation of 30 ± 2 ppm of nitric oxide was associated with minimal change in pulmonary vascular resistance ($p = 0.096$) (Table II).

DISCUSSION

We found a definite relation between trough cyclosporine levels and systemic vascular resistance in 34 heart transplant recipients. In contrast, no such relation existed between renal function and vascular resistance, or between cyclosporine levels and renal function in this small group of patients.

Our findings are consistent with the observation that cyclosporine acutely reduces blood flow to many organs,[7] and inhibits relaxation[17] or increases contractility of blood vessels,[9,10] or both. Cyclosporine can induce sustained systemic sympathetic neural activation with systemic hypertension.[18] It may block the effect of inhaled nitric oxide, thought to be an endothelium-derived relaxing factor,[19] on pulmonary circulation, but not the effect of prostacyclin on systemic circulation. We suspect that this may reflect the same mechanism demonstrated in cyclosporine-mediated attenuation of nitroprusside vasodilatation by others.[13]

Dependence of pulmonary vascular resistance on age has previously been described in normal volunteers[20] and is consistent with our findings by multivariate analyses.

The relation of cyclosporine trough blood levels to heart rate may reflect the known inhibitory effect of cyclosporine on adenosine diphosphate–stimulated respiration in the mitochondria, a reduction in the acceptor-control index (the ratio of the respiration rate with and without the presence of adenosine diphosphate) and reduction of mitochondrial oxidation of succinate.[21]

The advantage of using cyclosporine whole blood trough levels versus plasma or serum is that whole blood is unaffected by assay temperature or hematocrit.[22] The advantage of the specific monoclonal assay is that it may help to avoid measurement of cyclosporine metabolites.

The response to prostacyclin is consistent with a blocking effect of cyclosporine on prostacyclin synthesis,[11,12] but not on its action on vascular smooth muscle,

TABLE I Univariate Analysis*

Variable	Coefficient	Standard Error	Probability
Serum cyclosporine	0.39	0.22	0.09
Whole blood cyclosporine	0.072	0.026	0.01
Plasma cyclosporine	0.28	0.12	0.027
Grade of rejection	3.35	7.44	0.66
Standardized cyclosporine	5.63	3.35	0.10
Time after operation	0.029	0.029	0.33
Preoperative hypertension	11.6	19.6	0.56
Preoperative pulmonary vascular resistance	0.38	0.46	0.42
Age of patient	0.75	0.71	0.30
Age of donor	0.62	0.82	0.46
Prednisolone dose	0.27	0.75	0.72
Azathioprine dose	0.037	0.20	0.86
Nifedipine dose	0.48	0.31	0.13
Furosemide dose	0.10	0.086	0.24
Serum creatinine	0.17	0.22	0.44
Creatinine clearance	0.32	0.34	0.35

* Univariate analysis of linear correlation with systemic vascular resistance against recorded variables, with preoperative pulmonary vascular resistance in Wood units, age in years, drug doses in milligrams, serum creatinine in mmol/liter and creatinine clearance in ml/min.

TABLE II Effects of Prostacyclin and Nitric Oxide

	No Prostacyclin	Prostacyclin (6 ng/kg/min)	Mean Difference	t	df	p Value
Pulmonary vascular resistance	1.23 (0.098)	1.14 (0.077)	−0.1	1.64	33	0.14
Systemic vascular resistance	13.7 (0.82)	10.8 (0.76)	−2.86	5.39	33	<0.0001
Cardiac index	4.34 (0.23)	4.95 (0.23)	0.62	4.79	33	<0.0001
Heart rate	97.9 (2.6)	99.5 (2.3)	3.74	4.07	33	<0.0001
	Air	**Nitric Oxide**	**Mean Difference**	**t**	**df**	**p Value**
Pulmonary vascular resistance	1.21 (0.094)	1.15 (0.079)	−0.08	1.70	30	0.096
Systemic vascular resistance	13.9 (0.89)	10.9 (0.82)	0.16	1.22	30	0.28
Cardiac index	4.2 (0.22)	4.16 (0.21)	−0.04	0.80	30	0.46
Heart rate	99.1 (2.6)	86.6 (2.6)	0.05	0.30	30	0.74

Mean ± standard error for pulmonary vascular resistance (mm Hg · min/liter) and systemic vascular resistance (mm Hg · min/liter). Cardiac index (liters/min/m^2) and heart rate (beats/min) between rest and with 6 ng/kg/min of prostacyclin. The same variables are given for subjects breathing air or nitric oxide (30 ppm) in air. Means and *t* values for a 2-tailed paired Student's *t* test are given with probability values.
df = degree of freedom.

mediated through cyclic adenosine monophosphate,[23] in contrast to the action of endothelium-derived relaxing factor, which is mediated through cyclic guanosine monophosphate.[24]

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Effects of Exercise Training on Cardiorespiratory Function in Men and Women >60 Years of Age

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This study reports the physiologic effects of up to 14 months of aerobic exercise in 101 older (>60 years) men and women. After an extensive baseline physiologic assessment (Time 1), in which aerobic capacity and blood lipids were measured, subjects were randomized to an aerobic exercise condition (cycle ergometry, 3 times per week for 1 hour), nonaerobic yoga (2 times per week for 1 hour), or a waiting list nonexercise control group for 4 months, and then underwent a second (Time 2) assessment. At the completion of the second assessment, all remaining subjects completed 4 months of aerobic exercise and were reevaluated (Time 3). Subjects were given the option of participating in 6 additional months of supervised aerobic exercise, and all available subjects completed a fourth assessment (Time 4) 14 months after their initial baseline evaluation. Results indicated that subjects generally exhibited a 10 to 15% improvement in peak oxygen consumption after 4 months of aerobic exercise training, and a 1 to 6% improvement in aerobic power with additional aerobic exercise training. On the other hand, subjects, especially men, continued to have improvements in submaximal exercise performance (i.e., anaerobic threshold). In addition, aerobic exercise was associated with an improved lipid profile; subjects participating in aerobic exercise for up to 14 months exhibited increased levels of high-density lipoprotein cholesterol. Maintenance of regular aerobic exercise for an extended time interval is associated with greater cardiovascular benefits among older adults than has been reported previously.

(Am J Cardiol 1991;67:633–639)

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This study was supported in part by Grant AG04238 from the National Institute of Aging, Bethesda, Maryland, and by Grant HL30675 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received September 13, 1990; revised manuscript received and accepted November 28, 1990.
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Previous studies suggest that exercise training in older persons may improve cardiovascular function.[1–4] However, there has been wide variation in the magnitude of the training effects, with gains in aerobic power ranging from 0%[5] to 38%.[6] These discrepant findings may be attributable to differences in the mode, frequency and duration of exercise training, as well as to other factors, such as gender, initial fitness level of subjects, and procedural differences. Some programs set the intensity of exercise based upon age-predicted maximal heart rate,[6–8] whereas others used measures of oxygen consumption ($\dot{V}O_2$).[2,9] Similarly, some studies required subjects to exercise continuously for 30 minutes,[3,10–12] whereas others had subjects exercise continuously for <5 minutes.[6] Many investigations have studied only men,[5,6] and training studies have lasted 5 to 52 weeks. Methodologic problems that may have contributed to inconsistencies in results include small sample sizes, lack of adequate control groups, systematic bias (e.g., only reporting data on subjects who demonstrate the greatest gains), and inclusion of subjects with concomitant medical problems.

In an initial pilot study,[10] we demonstrated that a 12-week exercise program was associated with a 10% improvement in functional work capacity. However, we did not measure $\dot{V}O_2$ and had no control group. Subsequently, we improved upon the pilot study by including a larger sample, screening for concomitant medical illness, randomizing subjects to nonexercise control groups, and measuring $\dot{V}O_2$. In our initial report,[13] we described the results of the first 4 months. The purpose of the present investigation was to assess the feasibility of a long-term structured exercise program for older adults, and to document the cardiovascular adaptations in this more recent subject sample, with up to 14 months of aerobic exercise.

METHODS

The methods of our longitudinal study are described in detail elsewhere.[13] In brief, 101 healthy subjects (51 women, 50 men) were studied over a 14-month period. Subjects ranged in age from 60 to 83 years (mean ± standard deviation 67.0 ± 4.9). All subjects were in good health but were not engaged in habitual exercise before study entry. Subjects underwent a baseline evaluation (Time 1) and subsequent evaluations at 4 months (Time 2), 8 months (Time 3) and 14 months (Time 4). The study protocol was approved by the Duke Medical

Center institutional review board, and informed consent was obtained from each subject.

Procedures: The Duke Aging and Exercise Study was conducted between 1985 and 1987. Subjects were randomly assigned to an aerobic exercise group (n = 33), a yoga-flexibility control group (n = 34), or a waiting list control group (n = 34) after the completion of an extensive psychologic and physiologic assessment battery.

Subjects in the aerobic group attended 3 supervised exercise sessions per week for 4 consecutive months. During the first 2 weeks, subjects were assigned 6-beat training ranges equivalent to 50% of their maximal heart rate (HR) reserve [(HR max − HR rest) 0.50 + HR rest][14] during an initial bicycle exercise test. At the start of the third week, the exercise prescription intensity was increased to 60% of maximal heart rate reserve. During the fourth week, training ranges equivalent to 70% of maximal heart rate reserve were assigned. This training range was maintained for the remainder of the training regimen. In addition to the progressive increase in intensity, the duration of cycle ergometry started at 8 minutes at the first session, and increased by 2 minutes each subsequent session. By the fourth week, all subjects were cycling for 30 minutes continuously at an intensity equivalent to 70% of maximal heart rate reserve. The subjects then engaged in brisk walking/jogging and arm ergometry at their prescribed training range for 15 minutes. Each aerobic exercise session began with a 10-minute warm-up exercise period and concluded with 5 minutes of cool-down exercises. Heart rates were monitored via radial pulses and were recorded, along with ratings of perceived exertion,[15] 3 times during each exercise session.

Subjects in the yoga group participated in 60 minutes of yoga exercises ≥2 times per week for 4 months. The supervised yoga classes provided a control group for the effects of social stimulation and attention from trainers, without producing an aerobic training stimulus.

Subjects randomized to the waiting list control group did not receive any form of treatment between Time 1 and Time 2 evaluations. They were instructed to maintain their usual physical activity habits and to refrain from initiating an exercise program for the 4-month period. Subjects in all 3 groups were told to maintain their regular dietary habits until completion of the study.

After the first 4 months, all subjects participated in 4 months of aerobic exercise using the aforementioned exercise protocol and underwent a third (Time 3) assessment. Although this study was originally intended to last for 8 months, many subjects requested that it be extended. Consequently, we provided subjects with the option of participating in 6 additional months of supervised aerobic exercise and all available subjects (regardless of whether they stopped after 8 or 14 months) underwent an assessment at Time 4.

Assessments: Blood pressure measurements were obtained by standard cuff sphygmomanometry while the subject was in the sitting position. Body weight was obtained by a standard balance scale. Levels of plasma triglycerides, total serum cholesterol, and low- and high-density lipoprotein cholesterol were determined from blood samples drawn between 0700 and 0900 hours after a 14-hour fast.

Cardiorespiratory fitness was measured by a maximal cycle ergometry test after a practice test (Fitron cycle ergometer, model no. F1000750, Cybex Lumex Inc.). The protocol, with a pedaling rate of 60 rpm, started at 150 kpm·min^{-1} and increased by 150 kpm·min^{-1} every 3 minutes. A 12-lead electrocardiogram (Hewlett Packard, model no. 1517A) was monitored continuously and heart rate recorded every minute. Blood pressure was measured by cuff sphygmomanometry at 3-minute intervals. Respiratory and oxygen consumption measurements were obtained with a System 4400 metabolic instrument (Alpha Technologies, Inc., Laguna Hills, California). Measurements of VO_2, carbon dioxide consumption, expired ventilation and end-tidal gas concentrations were measured breath-by-breath and recorded every 15 seconds. In addition, anaerobic threshold was derived from the respiratory and oxygen consumption data, and was determined by a single, blinded investigator (MBH) unaware of the training status of the subjects by procedures described previously.[16]

Statistical analysis: Data were analyzed by a 3 (group) × 2 (gender) × 2 (time) repeated measures multivariate analysis of variance. Group and gender served as between-subject factors and time served as a within-subject factor. For the comparison between Times 3 and 4 (the optional 6-month extension), subjects were grouped according to status (whether or not they participated in the 6-month supervised aerobic exercise program) rather than by their initial group assignment.

RESULTS

Compliance: Of the original 101 subjects, 97 completed their assessments at Time 2. All remaining subjects participated in aerobic exercise between Times 2 and 3 and completed an average of ≥44 sessions, maintaining their heart rates within the prescribed training range ≥70% of the time. Only 8 subjects dropped out before completing their Time 3 assessments, for an 8-month dropout rate of 11%. Fifty subjects participated in an additional 6 months of aerobic exercise, 49 of whom completed the 6-month extended exercise program.

All available participants, regardless of compliance with the exercise program, were asked to return for a fourth assessment 14 months after the initial baseline evaluations. Eighty-four subjects returned, for an overall follow-up rate of 84% at 14 months. Compliance with the program is summarized in Table I.

Weight and blood pressure: A series of analyses of variance were performed to assess changes in body weight, and systolic and diastolic blood pressure between Times 2 and 3 and 3 and 4. Because the results

TABLE I Exercise Compliance

	Time 1 to Time 2			Time 2 to Time 3			Time 3 to Time 4		
	Aerobic	Yoga	Waiting List	Aerobic	Yoga	Waiting List	Aerobic	Yoga	Waiting List
Mean number ± SD of sessions attended	46 ± 2	32 ± 3	—	44 ± 4	45 ± 2	44 ± 3	52 ± 16	56 ± 7	53 ± 1
Percentage of time in training range	88	—	—	85	70	75	81	59	82
Mean RPE ± SD	13.5 ± 1.8	—	—	13.0 ± 2.2	13.9 ± 1.8	13.5 ± 2.3	13.1 ± 1.9	14.3 ± 2.5	13.5 ± 3.1
Dropouts / Total no. of pts.	2/33	0/34	2/34	3/31	3/34	1/32	0/23	0/12	1/15

49 subjects completed the aerobic exercise program at Time 4, but 84 of the original cohort of 101 subjects returned for follow-up evaluation.
RPE = ratings of perceived exertion; SD = standard deviation.

between Times 1 and 2 have been described previously, they will not be reported in detail. For body weight, there were significant gender main effects at Times 2 to 3 ($p < 0.0001$) and Times 3 to 4 ($p < 0.0001$). Overall, men weighed more than women (80.3 ± 9.6 vs 63.1 ± 10.4 kg). There also were significant time-related main effects between Times 2 and 3 ($p < 0.003$), but not between Times 3 and 4. All subjects tended to lose a slight amount of weight (<1.5 kg) between Times 1 and 4.

Between Times 1 and 2, men tended to exhibit a greater reduction in diastolic blood pressure than women. Systolic blood pressure did not change significantly. The analysis of variance between Times 2 and 3 revealed a time main effect, with all subjects exhibiting a reduction in diastolic blood pressure from 76 ± 9 to 73 ± 10 mm Hg ($p < 0.03$). Between Times 3 and 4, there was only a significant gender main effect for systolic blood pressure, with men having lower levels (124 ± 15) than women (129 ± 16) ($p < 0.03$). Comparison of blood pressures between Times 1 and 4 revealed significant time main effects for systolic ($p < 0.003$) and diastolic blood pressure ($p < 0.006$). Thus, there was a tendency for blood pressure to be lower at the conclusion of the study, independent of exercise status.

Cardiorespiratory function: Separate, repeated measures multivariate analysis of variance were performed between Times 2 and 3 and 3 and 4. Between Times 1 and 2, we reported that participants in the aerobic group achieved an average 11.6% improvement in peak $\dot{V}O_2$ (relative) and 9.1% improvement in anaerobic threshold, whereas results of subjects in the 2 other groups did not change. Thus, the different treatment programs produced differential improvements in cardiorespiratory fitness among the 3 groups.

Because all subjects participated in aerobic exercise between Times 2 and 3, the repeated measures multivariate analysis of variance for the Time 2 to 3 data assessed the effects of an additional 4 months of aerobic exercise for the aerobic group and of an initial 4 months of aerobic exercise for the yoga and waiting list control groups. The results of the multivariate analysis of variance yielded significant multivariate main effects for group ($p < 0.002$), gender ($p < 0.0001$) and time ($p < 0.0001$), and significant group × gender ($p < 0.02$), gender × time ($p < 0.06$) and group × time ($p < 0.0006$) interactions. Significant univariate group × time effects were observed for heart rate at submaximal work loads ($p < 0.04$), time on the bicycle ($p < 0.0001$), and peak $\dot{V}O_2$ ($p < 0.002$). Between Times 2 and 3, the yoga and wait list groups significantly increased their cardiorespiratory fitness, whereas the aerobic group merely maintained their previous improvements from Times 1 and 2 (Table II). Examination of the mean change in peak $\dot{V}O_2$ (relative) from Time 2 to 3 revealed that the yoga group achieved an average 10.5% improvement and the waiting list group an average improvement of 15%. Subjects in all 3 groups achieved a significant increase in anaerobic threshold ($p < 0.005$).

Because not all subjects elected to continue with 6 months of supervised exercise, exercise status was substituted for group in the multivariate analysis of variance as a between-subjects factor between Times 3 and 4. Table III lists the changes as a function of status. Results revealed a significant multivariate main effect for gender ($p < 0.0001$), which reflects the consistent advantage in aerobic capacity for men throughout the duration of the study, and a multivariate time × status interaction ($p < 0.002$). Men achieved higher peak $\dot{V}O_2$ than women (25.0 ± 8.2 vs 17.3 ± 2.8 ml/kg/min), had lower heart rates at rest (70 ± 14 vs 74 ± 11 beats/min) and at 300 kpm·min^{-1} (87 ± 12 vs 108 ± 16 beats/min), and achieved longer times on the bicycle (14.5 ± 5.0 vs 8.9 ± 1.4 min). Men also had greater anaerobic thresholds than women (13.4 ± 2.5 vs 10.6 ± 1.5 ml/kg/min). Examination of the univariate time × status interactions revealed that subjects who continued with the program exhibited lower submaximal heart rates ($p < 0.03$) and achieved longer bicycle times ($p < 0.005$) than subjects who discontinued the supervised exercise (Table III).

Interestingly, between Times 1 and 4 there was a significant time × status interaction ($p < 0.02$), as well as a significant time × status × gender interaction for anaerobic threshold ($p < 0.05$). Subjects who maintained their exercise increased their anaerobic threshold from 746 ± 240 to 940 ± 317 ml/min, whereas the subjects who did not continue only increased their thresholds from 749 ± 212 to 815 ± 243 ml/min. This pattern was especially true for the men who continued

TABLE II Mean Change ± Standard Deviation in Cardiorespiratory Function over Time by Group

Times	Aerobic 1	Aerobic 2	Aerobic 3	Aerobic 4	Yoga 1	Yoga 2	Yoga 3	Yoga 4	Waiting List 1	Waiting List 2	Waiting List 3	Waiting List 4
	(n = 32)	(n = 31)	(n = 28)	(n = 28)	(n = 34)	(n = 34)	(n = 31)	(n = 27)	(n = 34)	(n = 31)	(n = 31)	(n = 26)
HR at rest (beats/min)	74 ± 11.3	70 ± 13.4	72 ± 10.8	72 ± 9.0	75 ± 11.9	73 ± 10.0	70 ± 9.5	72 ± 10.6	70 ± 13.7	68 ± 14.2	69 ± 14.0	71 ± 12.6
Submaximal HR (beats/min)	104 ± 17.7	98 ± 14.2	98 ± 16.2	95 ± 14.9	105 ± 16.0	103 ± 15.9	96 ± 16.0	98 ± 16.1	103 ± 23.4	104 ± 24.7	98 ± 20.5	99 ± 22.7
Maximal HR (beats/min)	150 ± 16.6	150 ± 18.8	150 ± 17.5	144 ± 19.2	148 ± 16.9	146 ± 17.1	142 ± 14.0	140 ± 14.5	148 ± 20.5	144 ± 19.5	142 ± 16.1	138 ± 24.3
Bicycle time (min)	11.3 ± 3.4	12.1 ± 3.3	12.5 ± 3.7	12.2 ± 3.9	11.0 ± 2.8	10.1 ± 2.2	11.1 ± 2.5	10.6 ± 2.3	10.6 ± 2.7	9.8 ± 2.7	11.1 ± 3.2	10.6 ± 3.2
AT (ml/min)	770 ± 242	840 ± 303	901 ± 298	983 ± 318	736 ± 228	729 ± 219	766 ± 209	808 ± 240	742 ± 210	740 ± 224	818 ± 226	865 ± 299
Peak $\dot{V}O_2$ (ml/kg/min)	19.5 ± 5.2	21.4 ± 5.8	21.6 ± 6.0	22.7 ± 6.0	18.8 ± 4.5	18.7 ± 4.8	19.8 ± 4.9	20.0 ± 4.7	18.4 ± 3.9	17.9 ± 4.2	20.4 ± 5.1	20.6 ± 5.4
Peak $\dot{V}O_2$ (ml/min)	1,452 ± 540	1,570 ± 564	1,600 ± 624	1,656 ± 610	1,354 ± 438	1,327 ± 433	1,390 ± 444	1,433 ± 481	1,345 ± 436	1,311 ± 478	1,450 ± 527	1,495 ± 578
AT/$\dot{V}O_2$	0.55 ± 0.09	0.55 ± 0.07	0.58 ± 0.09	0.60 ± 0.09	0.55 ± 0.06	0.55 ± 0.08	0.56 ± 0.09	0.59 ± 0.15	0.56 ± 0.10	0.58 ± 0.06	0.56 ± 0.09	0.60 ± 0.09

AT = anaerobic threshold; HR = heart rate; $\dot{V}O_2$ = peak oxygen consumption.
Time 1 and Time 2 data have been reported previously.[13]

to exercise. The men who participated in the exercise program increased their thresholds from 914 ± 209 to 1,223 ± 190 ml/min ($p = 0.0001$), whereas the thresholds of the men who discontinued remained relatively unchanged (894 ± 192 to 965 ± 275 ml/min) (difference not significant). Corresponding values were 570 ± 106 to 618 ± 118 and 601 ± 90 to 684 ± 135 ml/min for women who continued and discontinued the program, respectively. Of the original 33 subjects assigned to the aerobic group, 23 participated in the full 14-month exercise program. This subgroup of subjects increased their aerobic power by 18% at the conclusion of the study.

Lipids: To assess changes in lipids, low- and high-density lipoprotein cholesterol, total cholesterol and triglycerides were considered together in a multivariate analysis of variance. The mean lipid values for the 4 testing sessions are listed in Table IV. In our previous report,[13] we noted that women had higher high-density lipoprotein levels (60.5 ± 14.3 mg%) than men (44.3 ± 8.9 mg%) ($p < 0.0001$), and that only the aerobic group had a significant reduction in total ($p < 0.002$) and low-density lipoprotein cholesterol ($p < 0.003$). The 3 groups had a significant reduction in triglycerides over time ($p < 0.009$).

Between Times 2 and 3, there were significant multivariate main effects for gender ($p < 0.0001$) and time ($p < 0.0001$). Both total ($p < 0.0001$) and low-density lipoprotein cholesterol ($p < 0.0001$) increased slightly from Time 2 to 3 in all groups. Once again, women had higher high-density lipoprotein cholesterol levels than men.

The multivariate analysis of variance between Times 3 and 4 revealed a marginally significant time × status interaction ($p < 0.06$), as well as significant main effects for time ($p < 0.0003$), gender ($p < 0.0001$) and status ($p < 0.05$). Examination of the univariate time × status interactions indicated that only the subjects who continued in the exercise program significantly increased their levels of high-density lipoprotein cholesterol (54.3 ± 14.7 to 58.0 ± 14.7 mg%; $p < 0.05$) (Table IV). No other univariate interactions were statistically significant.

DISCUSSION

The results of this study demonstrate that a program of regular aerobic exercise is associated with significant improvement in functional capacity in a group of older men and women. Men and women had comparable improvements of 10 to 15% in cardiorespiratory fitness after 4 months of aerobic exercise. An additional 4 months of exercise produced a more gradual improvement of 1 to 6% in peak aerobic power. Subjects in the aerobic group who maintained their exercise for the full 14 months achieved an average increase in peak $\dot{V}O_2$ of 18%, relative to their baseline assessments. It should be emphasized that these data reflect the average improvement among highly motivated older persons who initiate an exercise program, rather than the potential physiologic responses to exercise training. Indeed, 1 subject achieved a 68% improvement in aerobic power. Even

TABLE III Mean Physiologic Measures ± Standard Deviation by Status (Discontinued or Continued for 6-Month Extension) for Time 1 (Baseline), Time 3 (8 Months) and Time 4 (14 Months)

	Discontinued			Continued		
Times	1	3	4	1	3	4
Cardiovascular						
HR at rest (beats/min)	74.2 ± 12.6	70.9 ± 11.3	74.6 ± 11.4	73.1 ± 12.3	70.7 ± 11.9	70.2 ± 9.8
Submaximal HR (beats/min)	104.7 ± 18.6	99.5 ± 18.4	103.5 ± 17.8	104.7 ± 19.7	97.0 ± 17.0	93.9 ± 17.3
Bicycle time (min)	11.0 ± 2.7	11.3 ± 2.9	10.3 ± 2.5	10.8 ± 3.3	11.8 ± 3.4	11.7 ± 3.6
Peak $\dot{V}O_2$ (ml/kg/min)	19.0 ± 4.2	19.9 ± 4.8	19.9 ± 4.6	18.6 ± 5.0	21.1 ± 5.7	22.0 ± 5.9
Peak $\dot{V}O_2$ (ml/min)	1,376.6 ± 424.9	1,400.3 ± 454.7	1,425.6 ± 491.6	1,373.3 ± 524.8	1,537.3 ± 589.0	1,602.1 ± 598.6
AT (ml/min)	748.7 ± 211.8	772.4 ± 224.2	814.5 ± 242.8	745.7 ± 239.7	865.8 ± 260.6	940.4 ± 317.3
Total cholesterol (mg%)	236.4 ± 36.5	254.4 ± 31.2	253.3 ± 38.0	233.5 ± 35.0	241.9 ± 38.8	235.1 ± 35.9
HDL cholesterol (mg%)	49.0 ± 13.9	52.3 ± 12.5	53.0 ± 14.8	54.8 ± 14.7	54.3 ± 14.7	58.0 ± 14.7
LDL cholesterol (mg%)	154.7 ± 35.1	173.2 ± 33.8	170.8 ± 39.9	152.3 ± 36.0	163.9 ± 35.6	155.6 ± 34.8
Triglycerides (mg%)	163.4 ± 62.3	144.7 ± 79.0	147.8 ± 69.8	131.8 ± 52.8	118.6 ± 61.6	107.4 ± 42.0

HDL = high-density lipoprotein; LDL = low-density lipoprotein; other abbreviations as in Table II.

greater improvements may be possible in some subjects with more intense training.

The magnitude of change in peak $\dot{V}O_2$ is generally consistent with other studies. Cunningham et al,[9] for example, reported an 11% improvement after 12 months in a randomized clinical trial of 224 men aged 55 to 65 years. Niinimaa and Shephard[17] observed a 10% improvement in maximal $\dot{V}O_2$ in 19 men and women aged 60 to 76 years. However, other studies have reported higher values. Sidney and Shephard[12] studied 14 men and 28 women for a period of up to 1 year of exercise training. Although they reported an overall 24% improvement in maximal $\dot{V}O_2$, only 22 of the 42 subjects actually completed the protocol. Because an additional 20% of the potential subjects were rejected at study entry, the authors noted that the improvement in aerobic capacity may not have been representative of the older population in general. Seals et al[2] reported a 25 to 30% increase in maximal $\dot{V}O_2$ after 12 months of training. However, they used a different exercise modality (jogging and walking vs biking) at a higher intensity training stimulus (85% for 45 vs 70% for 30 minutes), and reported data from only the 11 subjects who completed the exercise training protocol. Similarly, Barry et al[6] noted a 38% increase in maximal $\dot{V}O_2$ after 3 months of exercise training in only 8 subjects aged 55 to 78 years. Inclusion of subjects <60 years old in the sample, reporting data only for those subjects who completed the exercise training protocol, and apparent premature termination of several initial tests may have influenced the magnitude of the training effect. In contrast, our data were analyzed following the "intention to treat" principle, under the assumption that it is more clinically relevant to assess the likely extent of improvement in aerobic power in healthy older persons than the potential degree of improvement.

Few previous studies examine the effects of exercise training on anaerobic threshold in older subjects. Seals et al[18] demonstrated a decrease in lactate levels at submaximal work loads after a 6-month exercise training program, and this effect was enhanced when a more intensive exercise regimen was continued for 6 additional months. Our study is unique in that it demonstrates progressive improvements in submaximal exercise performance with prolonged training at the same intensity level.

It is also of interest to note that continued exercise training appeared to increase anaerobic threshold more than peak $\dot{V}O_2$. Examination of the ratio of anaerobic threshold to peak $\dot{V}O_2$ revealed an increase from 54% at Time 1 to 60% at Time 4 among participants who continued to exercise for the 14 months. These data are consistent with data from studies of middle-aged sedentary persons, which showed that the anaerobic threshold occurs at 50 to 60% of maximal $\dot{V}O_2$.[19] In addition, the change in the ratio of anaerobic threshold to $\dot{V}O_2$ suggests that increases in anaerobic threshold and peak $\dot{V}O_2$ initially occur in parallel but then dissociate with prolonged training. For example, the correlation of the change in anaerobic threshold and change in peak $\dot{V}O_2$ among aerobic participants was significantly greater between Times 1 and 2 ($r = +0.65$, $p < 0.001$) than for aerobic participants who maintained their aerobic exercise between Times 3 and 4 ($r = +0.26$, difference not significant). The observation of a dissociation between increases in anaerobic threshold and peak $\dot{V}O_2$ among the elderly has been noted previously in young and middle-aged subjects.[20,21] Peripheral adaptations that promote increased submaximal exercise performance may include increased capillarization or increased aerobic enzyme content in skeletal muscle.[22] Thus, maintenance of regular aerobic exercise is associated with significant

TABLE IV Mean Lipid Values ± Standard Deviation

Times	Aerobic				Yoga				Waiting List			
	1	2	3	4	1	2	3	4	1	2	3	4
	(n = 32)	(n = 31)	(n = 28)	(n = 27)	(n = 34)	(n = 34)	(n = 30)	(n = 30)	(n = 34)	(n = 32)	(n = 31)	(n = 27)
TC (mg%)	235 ± 38.6	224 ± 39.4	247 ± 36.9	238 ± 33.4	233 ± 29.5	242 ± 33.2	250 ± 28.2	248 ± 30.7	236 ± 38.2	232 ± 43.7	246 ± 42.2	242 ± 48.0
HDL–C (mg%)	52.7 ± 15.4	52.3 ± 14.3	55.2 ± 13.6	56.7 ± 15.5	49.5 ± 12.3	52.2 ± 13.1	51.2 ± 14.2	52.4 ± 13.9	53.4 ± 16.0	54.5 ± 15.6	53.8 ± 13.4	58.9 ± 14.9
LDL–C (mg%)	151 ± 39.1	144 ± 38.9	166 ± 39.9	156 ± 34.1	155 ± 28.4	165 ± 32.2	173 ± 27.5	171 ± 30.0	153 ± 39.0	150 ± 41.0	165 ± 37.1	158 ± 47.2
TRIG (mg%)	153 ± 71.7	139 ± 83.2	126 ± 73.9	123 ± 71.6	143 ± 55.5	125 ± 61.2	129 ± 67.3	126 ± 52.8	144 ± 49.1	138 ± 60.4	136 ± 73.1	124 ± 51.5

TC = total cholesterol; TRIG = triglycerides; other abbreviations as in Table III.
Data at Time 1 and Time 2 have been reported previously.[13] Only 12 women (5 aerobic, 2 yoga, 5 waiting list) were receiving hormone-replacement therapy. Removal of these women from analysis did not alter the results.

improvements in aerobic power and, perhaps more importantly, with increased ability to exercise at submaximal work loads.

We also noted significant changes in lipid profiles associated with the exercise training program. We observed that subjects who participated in aerobic exercise had a reduction in total and low-density lipoprotein cholesterol between Times 1 and 2. Moreover, subjects who continued for 14 months of exercise also had a significant increase in high-density lipoprotein cholesterol. Our data are generally consistent with cross-sectional[23,24] and longitudinal studies[25,26] among younger adults, although studies have not always found lipid changes.[27,28] Our data are consistent with those of Brownell et al,[29] who reported that women tended to have lower total and low-density lipoprotein cholesterol values and higher high-density lipoprotein cholesterol values than men. Although Brownell et al noted a trend for men to have larger decreases in low-density lipoprotein cholesterol and larger increases in high-density lipoprotein cholesterol, relative to women, after 10 weeks of exercise, we did not observe a similar trend in our data. In the absence of any gender interactions with group or time, it would appear that, in our sample of older men and women, the lipid changes in response to exercise were comparable. Thus, aerobic exercise is associated with significant and meaningful improvements in aerobic capacity, submaximal exercise performance, and lipid patterns, particularly when habitually maintained.

Acknowledgment: We wish to thank Janet Simon, Robin Pomeroy, Julia Whitaker, Cheri Rich, Sally Schnitz and Carol Cracchiolo for technical assistance, and Janet Ivey for secretarial assistance.

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A Plea for Two Actions That Need to be Taken

Norman M. Kaplan, MD

I wish to use this forum to encourage every reader to take 2 positive steps for their patients' (and their own) welfare.

First, every person in the U.S. should be asked to complete a living will, durable power of attorney, and organ donation authorization, as provided in the single-page Medical Directive in Emanuel and Emanuel's report in the June 9, 1989 *Journal of the American Medical Association* (JAMA).[1] Their single document provides a simple solution to the major problem left unsettled by the original U.S. Supreme Court's decision not to allow the parents of Nancy Cruzan to remove life support in the absence of her written authorization. The use of the directive has been explored further in a more recent JAMA report.[2] Hopefully, the American Medical Association will make copies of the directive available but, in the interim, page 3290 of the June 9, 1989 JAMA can be reproduced and used.

Only 15% of the U.S. public now has a living will. Every health professional should, first, complete such a directive for him- or herself and, second, ensure that every patient under their care be provided such a document. Those of us at a medical school should insist that the topic be discussed with our students and staff and that they be offered a directive. Those of us at hospitals and clinics should ensure that all patients and their families have access to a directive, preferably *before* admission, while they are outpatients.

If we do not take such action, many more than the currently estimated 30,000 patients in the U.S. who are comatose and in a persistent vegetative state will be denied the right to have unwanted life support removed. The point, of course, is that every person has the obligation to express their wishes, even if those wishes be that every conceivable action be taken to support life under any circumstance. I hope that every medical society, hospital staff and medical school faculty will do all that is possible to enlarge this practice.

The second action is much more positive than the first and it also applies to a very large part of the population. This involves the use of postmenopausal estrogen therapy, a practice that is being curtailed in part because of an incorrect assumption that it will aggravate or incite systemic hypertension, along with concerns about the induction of endometrial cancer.

Postmenopausal estrogen replacement therapy has been repeatedly and almost uniformly shown to reduce morbidity and mortality from coronary artery disease[3] and stroke[4] with an overall reduction in risk close to 50% of that seen in non-users. The one negative report that conflicts with the overwhelming strong positive data from >24 others is from the Framingham Heart Study.[5] In that cohort, estrogen users had a 1.90 increased relative risk of coronary artery disease and a 2.27 increased relative risk of stroke compared to non-users. Although there is no apparent reason for these highly discrepant results, there are problems with these data, mainly in the ascertainment of estrogen use, its duration and dosage, and time relative to the onset of menopause.

The cardioprotective effect of estrogens has generally been ascribed to favorable influences on lipids.[6] A study in monkeys has shown that estrogens also modulate the vasomotor responses of coronary arteries, presumably by maintaining the integrity of the endothelial cells.[7]

Postmenopausal women with preexisting systemic hypertension obtain relatively more protection from coronary artery disease by estrogen therapy than those who are normotensive, presumably because they start at a significantly higher risk. In the study of Ross et al,[3] the mortality rate from coronary artery disease in those who were not hypertensive was 3.2/1,000 persons per year in non-users and 2.2 in users, a 32% reduction; in those who were hypertensive, the rates were 6.5 in never-users and 3.1 in users, a 52% reduction.

Beyond the almost certain and highly significant protection against cardiovascular disease offered by postmenopausal estrogen use, it will also protect against the very considerable risk of bone fractures from osteoporosis, a risk that is >50% for a 50-year-old white woman who does not use estrogens during her remaining lifetime.[8]

The only downside of postmenopausal estrogen use has been the potential for endometrial cancer in women with an intact uterus. This risk has been virtually removed by concomitant use of progestogens for 10 to 12 days each month. The risk for breast cancer does not appear to be increased.

As summarized by Belchetz[9] in an editorial: "Hormone replacement treatment is not a panacea, and healthy bones and hearts may be achieved by exercise and diet. But there is now irrefutable evidence of the benefits of this treatment, and it should be offered to many more women." He had previously noted that the therapy was less widely used than it should be because "many doctors remain suspicious that thrombotic disorders are promoted by estrogens; they wrongly extrapo-

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late from the experience of younger women who take oral contraceptives."

Belchetz should have added a concern about the promotion of hypertension as well, also wrongly extrapolated from the effects of oral contraceptives. I believe that this too is a widely held view. Nonetheless, beyond a handful of cases,[10] numerous surveys[11-15] have shown no promotion of hypertension by postmenopausal estrogen use. In fact, lower blood pressures have been found in postmenopausal estrogen users than in non-users in all 5 of these surveys.

Menopause is accompanied by a steeper increase in blood pressure[16] and a considerably higher risk of coronary artery disease.[17] In view of the strong evidence that estrogen use will protect against coronary artery disease and may indeed reduce blood pressure, the need for postmenopausal estrogen therapy is clear. We need to remove any concerns about the potential for the promotion of systemic hypertension by this therapy so it may be more widely provided to those in need.

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Is ST Elevation the Only Electrocardiographic Response of the Ischemic Right Ventricle?

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Right ventricular (RV) infarction is frequently associated with transient ST elevation in right precordial leads.[1,2] Studies of patients with an inferior infarction have shown that right precordial ST elevation is predictive of a proximal right coronary artery (RCA) occlusion,[3] and that the duration of the ST elevation is predictive of the extent of early RV dysfunction.[4] The spectrum of electrocardiographic response to ventricular ischemia is well described in the left coronary distribution[5-7] but not in the RCA distribution. Stenosis of the proximal RCA before the major RV branches is uniformly associated with exercise-induced right precordial ST elevation.[8-10] Proximal RCA lesions have also been associated with a reduction in RV ejection fraction during exercise and during balloon occlusion.[11,12] Two studies of 8 and 13 patients undergoing RCA angioplasty showed right precordial ST elevation, but did not report the occurrence of right precordial ST depression.[13,14]

This study was performed prospectively to determine the electrocardiographic response in V_4R in consecutive patients undergoing coronary angioplasties, using angioplasty as a model of reversible ischemia. We hypothesized that ischemia during proximal RCA angioplasty would be similar to exercise-induced ischemia—that is, ST elevation and not ST depression would be seen in the right precordial leads.

A total of 139 patients (26 women, 113 men) with 179 lesions were prospectively studied. The patients were referred for percutaneous transluminal coronary angioplasty for both stable and unstable angina pectoris to 3 affiliated University of Colorado hospitals over a period of 14 consecutive months. Every patient who did not have bundle branch block and on whom a V_4R lead was placed was analyzed. One vessel was dilated in 110 patients, 2 vessels were dilated in 25, and 3 vessels were dilated in 4. Table I lists the anatomical distribution.

Right precordial V_4R was recorded before, during and after balloon occlusions. Paper speed was 50 mm/s and the calibration was 1 mV = 10 mm. ST-segment deviation was measured immediately before balloon deflation, at 80 ms after the J point. Three consecutive beats were analyzed, with the ST deviation measured visually to the nearest 0.25 mm. The mean value was calculated, with a cut off of ST deviation of 1 mm required. Balloon inflations of ≥45 seconds (majority ≥60 seconds) were analyzed.

There were 35 patients who had stenoses of ≥70% before the majority of the RV blood supply (nearly all before the first RV branch; the others after a small first RV branch and before a larger second RV branch). Of 35 patients, 29 (86%) had ≥1 mm of ST elevation in V_4R with balloon inflation. Of the 15 patients with distal RCA lesions, none had ST elevation in V_4R during balloon inflation. There were 85 left anterior descending or large ramus intermedius stenoses dilated. The great majority (92%) were proximal lesions, at or before the first diagonal branch. Seven of the left anterior descending lesions and 3 of the trifurcation lesions produced ST elevation in V_4R, whereas no ST elevation was revealed in the other 75. Only 9 of these 75 left anterior descending lesions produced mild ST depression and, occasionally, accompanying T-wave inversion. Of the 41 circumflex distribution stenoses, ST elevation in V_4R was revealed in 3, and nearly one-third had ST depression with frequent T-wave inversion. Three "protected" left main stenoses were dilated, and no significant ST changes in V_4R were revealed in any of them.

In an earlier study we showed that proximal RCA stenosis may result in exercise-induced RV ischemia as well as inferior left ventricular ischemia.[8] Although exercise-induced ischemia of the left ventricle is most often represented as ST depression, we did not see ST depression in V_1 during exercise in patients with RCA disease, only ST elevation.[8] This suggested that RV ischemia may only be manifested as ST elevation. We used percutaneous transluminal coronary angiography as a model of reversible ischemia to determine if RV ischemia ever resulted in ST depression in the right precordial leads. It is known that ischemia of the left ventricle during balloon inflation often results in either ST elevation or depression in left precordial leads.[5-7] This study demonstrates that RV ischemia during percutaneous transluminal coronary angioplasty, just as during exercise, results only in right precordial ST elevation and not ST depression.

The absence of ST elevation in V_4R in 6 of the 35 proximally diseased RCA patients has several possible explanations. Rotation of the heart or unusual body geometry may alter the sensitivity of the precordial leads. Some investigators advocate using extreme right precor-

TABLE I ST-Segment Change in V_4R During Angioplasty

Coronary Angioplasty Site	ST-Segment Change in V_4R*		
	Elevation	Depression	None
Proximal right	29	0	6
Distal right	0	0	15
Left circumflex	3	13	25
Left anterior descending	10	9	66
Left main	0	1	2

* Minimum of 1 mm of ST-segment change.

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Manuscript received June 11, 1990; revised manuscript received and accepted November 14, 1990.

dial leads, V_4R to V_8R,[14] or intracoronary recording[7] for the best sensitivity. Collateral vessels, not present in any of the 35 proximally diseased RCA patients or the 15 distally diseased RCA patients, could be transiently opened during balloon inflation and thereby alleviate RV ischemia. Historically, right precordial leads have only reached a 90% sensitivity when compared with wall motion and hemodynamic correlation.[1]

The "false positive" ST elevation in V_4R seen with some proximal left anterior descending and proximal circumflex angioplasties is probably multifactorial. Pure posterior-lateral subendocardial ischemia, seen reciprocally as ST elevation anteriorly, may explain the circumflex and high diagonal distributions. Norell[6] studied 27 patients with 1-vessel coronary artery disease involving the proximal left anterior descending artery, and found the subset of patients with accompanying inferior ST depression did not have any change in inferior wall motion. Such "reciprocal" changes have likewise been revealed during angioplasty of circumflex lesions. Berry et al[5] showed that the majority of circumflex angioplasties revealed ST depression on the surface precordial leads, whereas the intracoronary electrocardiogram primarily revealed ST elevation. Widespread left precordial ST elevation "spilling over" to the right precordium probably explains the majority of cases involving the left anterior descending artery. This is akin to anterior infarction, where the trend of the precordial ST elevation is diagnostic, growing from V_1 to V_3.[15]

ST depression in V_4R during left coronary artery angioplasty probably has several explanations. Angioplasty of the circumflex system can result in posterior wall transmural ischemia with ST elevation, and reciprocal ST depression in the anterior leads. ST depression in V_4R during left anterior descending artery angioplasty probably represents subendocardial ischemia of the anterior wall that is detectable into the right precordium.

In the absence of intervention, persistent ST elevation with left ventricular infarction usually results in Q waves and a decreased left ventricular ejection fraction that does not improve over time. As shown by Yasuda et al[16,17] and many others, serial evaluation of clinically diagnosed RV infarctions demonstrates a progressive improvement in ejection fraction after infarction, implying significant reversible RV dysfunction. Combined with the ST elevation as the only electrocardiographic response of RV ischemia by treadmill and angioplasty studies, one could question whether much of what is called "RV infarction" is in fact reversible ischemia. Because of its thinness, better coronary phasic flow, better wall tension characteristics, and the possible role of Thebesian veins, the right ventricle tolerates ischemia better than the left. Schofer et al,[18] comparing intracoronary thallium with pyrophasphate injections in patients with an acute myocardial infarction, likewise concluded that the right ventricle does not infarct under conditions similar to those under which the left ventricle infarcts.

Pathologic correlation of right precordial ST elevation in RV infarction is scant. Isner and Roberts[19] described a pathologic classification of RV infarctions. In their series, 27 of 33 involved only the posterior ventricles and posterior septum, and only 7 extended into the anterior RV free wall. Although their work predated right precordial electrocardiographic correlation, it is probable that the large majority of the 33 RV infarctions would have had acute right precordial ST elevation. Yet only 18% resulted in infarction of the RV free wall. This lends support to the current hypothesis that substantial reversible RV ischemia is often present when RV infarction is clinically diagnosed during acute inferior infarction.

Thus, among RCA angioplasties, only ST elevation occurred in V_4R. No ST depression in V_4R was demonstrated during the 50 RCA angioplasties. These data, combined with previous exercise data, support these concepts: (1) RV free wall ischemia induced by either exercise or angioplasty results in right precordial ST elevation; (2) ST elevation may be the only electrocardiographic response of the ischemic RV free wall; and (3) much of what is called RV infarction may actually be reversible RV ischemia.

Acknowledgment: We gratefully acknowledge the contributions of Barry Molk, MD, Robert Baum, MD, and Jerry Greenberg, MD, and the expert secretarial assistance of Ferrill Murray and Karen Mileham.

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Differentiating Anginal Patients with Coronary Artery Disease from Those with Normal Coronary Arteries Using Psychological Measures

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Up to 30% of patients with chest pain who undergo coronary catheterization have angiographically normal coronary arteries.[1] Several recent prospective studies have shown that patients who are found to have normal coronary arteries score consistently higher than patients with coronary artery disease (CAD) on measures of the personality dimension of neuroticism when measured at catheterization[2-4] or 1 year after.[5] These findings are based on a diverse set of psychological tests, including the Minnesota Multiphasic Personality Inventory, Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory, Eysenck Personality Questionnaire, Cornell Medical Index, and the Millon Behavioral Health Inventory, attesting to the reliability and validity of the association between normal coronary arteries and neuroticism.

Anticipating these findings linking neuroticism and chest pain with minimal, if any, intimal irregularities of the coronary arteries, Costa[6] raised the possibility that psychometric information might be helpful to physicians in evaluating candidates for angiography. If a sensitive and specific psychometric scale could be developed to determine that the patient is likely to have normal coronary arteries, then less invasive alternatives to catheterization might be recommended. As a first step, we initiated this prospective study to evaluate the usefulness of an inventory that was developed for use in medical settings to differentiate chest pain patients.

Referred for cardiac catheterization with a preliminary diagnosis of atherosclerotic CAD, 115 men consented to participate in the study. Routine catheterization procedures were not altered for this study.[7] Of the 115 patients, 28 (24%) were found to have <50% stenosis of their coronary arteries (normal artery group). The remaining 87 patients were found to have >50% stenosis of ≥1 coronary artery (CAD group). The mean ages (56 years) of the patients in these 2 groups did not differ significantly.

The day before catheterization, all patients completed the Millon Behavioral Health Inventory (MBHI), a 150-item (true/false) survey developed to aid in the psychological understanding of medical patients.[8] The MBHI yields 20 scale scores; for the present discriminant analysis, we used the 6 "psychogenic attitude scales" (chronic tension, recent stress, premorbid pessimism, future despair, social alienation and somatic anxiety) and the 3 "psychosomatic scales" (allergic inclination, gastrointestinal susceptibility and cardiovascular tendency). The 11 scales we excluded assess "basic personality style" and "prognostic possibilities." Our focus on the 9 scales that measure neuroticism was not only consistent with recent findings but also enabled us to adhere to the general standard of 10 subjects per "item" for conducting a discriminant analysis.[9]

The relation between the 9 MBHI scale scores and normal coronary arteries versus CAD classification was assessed by a direct discriminant analysis using the Statistical Package for the Social Sciences. A single significant function (canonical $R = 0.47$; Wilks' lambda $= 0.78$; chi-square $(9) = 26.89$, $p = 0.002$) distinguished the groups. Scores on the discriminant function correlated ($r > 0.30$) with scores on the following MBHI scales: somatic anxiety, cardiovascular tendency, chronic tension, gastrointestinal susceptibility, recent stress and allergic inclination. The mean function score of the normal coronary artery group (0.93) was higher than that of the CAD group (−0.30). When the discriminant function was used to classify patients into the 2 groups based on their MBHI responses, with the prior probabilities of group size, 82% of the patients were correctly assigned to their appropriate group. The assignment of the patients with CAD was more accurate (97% correct) than the assignment of the patients with normal coronary arteries (36% correct).

On the basis of psychometric assessments administered before coronary angiography, we can distinguish between patients with chest pain who are subsequently determined to have coronary artery disease or normal coronary arteries. These findings of higher neuroticism of the patients with normal coronary arteries support our

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expectations based on recent findings.[2-5] However, the usefulness of the MBHI for psychometric screening is less clear. The accuracy of the predictive model based on our application of the MBHI is not sufficient, given the consequences of false negative classification for CAD. However, these preliminary findings lead us to believe that with further research a more accurate psychometric instrument could be developed that would be sensitive and specific for differentiating normal coronary arteries from CAD likelihood. In addition, auxiliary measures could be used to improve further the accuracy of identifying patients with normal coronary artery. For example, Engel et al[10] asked 83 patients to complete forms describing their chest pain for 2 to 3 weeks before catheterization. Subsequently, they found that chest pain with exertion correlated positively with CAD, whereas chest pain during emotional arousal did not correlate with CAD but correlated positively with neuroticism.[4] Descriptions of feeling angry, annoyed, tense, worried and upset were positively associated with neuroticism but not with CAD. Their findings and ours suggest that a full behavioral assessment, including measures of neuroticism and descriptions of chest pain, could yield significant diagnostic information.

Pryor et al[11] developed a model for estimating the likelihood of significant CAD based on 9 noninvasive clinical characteristics, such as pain type, hyperlipidemia, smoking history and S-T-wave changes. Our data support the addition of neuroticism measures in considering the likelihood of CAD. Validation of our findings using a more precise psychometric instrument would lead us to encourage physicians to consider such measures in their evaluation of patients with chest pain. Should other clinical signs point toward the presence of CAD, and should there be minimal evidence of neuroticism, then we recommend proceeding with coronary angiography. However, if there is psychometric evidence of neuroticism in a symptomatic patient, we suggest that additional noninvasive tests, such as cardiac fluoroscopy or stress thallium scintigraphy, be conducted before considering coronary angiography. Given recent findings[12] of a possible relation between esophageal and psychiatric abnormalities in patients with chest pain but with normal coronary arteries, we also suggest that esophageal function be evaluated.

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Lidocaine Toxicity After Subcutaneous Infiltration in Children Undergoing Cardiac Catheterization

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The administration of subcutaneous lidocaine as a local anesthetic is readily observed in dental, orthopedic, and minor surgical procedures as well as for the insertion of monitoring catheters. The use of any local anesthetic presents significant risk to the patient, and extreme caution should be exercised in its administration.[1] Significant complications resulting from lidocaine toxicity have been reported.[2–5] However, it is not well recognized that an elevated serum lidocaine level may result from the subcutaneous infiltration of lidocaine. Although the guidelines for the subcutaneous infiltration of lidocaine are established for children, these recommendations are often exceeded. In our study of 10 sequential patients, we describe 2 cases of lidocaine toxicity that occurred in children undergoing cardiac catheterization. This study was designed to determine if elevated serum lidocaine levels could occur after subcutaneous infiltration in children.

Before the cardiac catheterization procedure, each child was premedicated with 1 mg/kg of diphenhydramine hydrochloride by mouth and 0.15 mg/kg of intramuscular morphine sulfate. The right and left inguinal areas were prepped with a povidone–iodine solution and then draped in a sterile manner. The skin and subcutaneous tissue of the right femoral triangle was then infiltrated with lidocaine hydrochloride. The concentration and volume of lidocaine administered were determined by the physician performing the catheterization. The syringe was aspirated frequently to avoid inadvertent intravascular injections of lidocaine. Cannulation of the right femoral vessels, the preferred site of entry, was attempted percutaneously with the Seldinger technique. When the right femoral vessels were unable to be entered, the left groin or left subclavian regions, or both, were anesthetized with the same technique. In 7 patients, an additional volume of lidocaine was necessary to provide adequate anesthesia. Whole blood samples (1.0 ml) were obtained via the femoral artery catheter and serum lidocaine levels were determined with the fluorescent polarization immunoassay technique 25 to 120 minutes (mean 75) after the most recent infiltration. In 6 infants and children with a body surface area <1 m^2 who received a mean dose of 19.6 mg/kg (range 4 to 47), 83% developed either therapeutic or toxic levels of lidocaine (2.4 to 7.2 μg/ml, mean 3.98) (Table I). In 4 children >1 m^2, all levels were ≤1.0 μg/ml (range 0.8 to 1.0, mean 0.95) after a mean dose of 3.59 mg/kg (range 3 to 5) of lidocaine. Multiple infiltrations of lidocaine required in children <1 m^2 created an increased likelihood of an elevated serum lidocaine level (p <0.001), demonstrating that infants <1 m^2 are at an increased risk of lidocaine toxicity, most likely because of their small body surface area, difficulty in cannulating and the need for adequate anesthesia.

The potential danger resulting from lidocaine overdose may not be fully appreciated. These cases represent the first documented reports of toxic serum lidocaine levels obtained after subcutaneous infiltration in children undergoing cardiac catheterization. Schwartz et al[6] reported that the peak mean lidocaine level occurred 30 minutes after subcutaneous infiltration and that no patient developed toxic levels. We suspect that because our lidocaine samples were obtained approximately 45 minutes after infiltration in patients 1 and 2, the measured lidocaine level may not reflect the actual peak level.

Alfano et al[5] described a case of lidocaine toxicity secondary to subcutaneous administration in a 2-year-old child, who received a total of 31 mg/kg of lidocaine to repair a superficial laceration in the right axillary area. Twenty minutes after the subcutaneous administration, the child had a grand mal seizure from which she recovered. In the 2 aforementioned children, difficulties obtaining access necessitated alternate sites of entry, or multiple injections of lidocaine, or both. The total dosage administered to these 2 patients (patient 1, 47 mg/kg; patient 2, 25 mg/kg) exceeds the current recommendations for the subcutaneous infiltration of lidocaine (4.5 mg/kg of lidocaine without and 7.0 mg/kg with epinephrine).[7] Although no seizures or permanent central nervous system disturbances were noted in either patient,

TABLE I Lidocaine Levels in Children Undergoing Cardiac Catheterization

Patient	Wt. (kg)	BSA (m^2)	CHF	Lidocaine Dose (mg/kg)	Level (μg/ml)	Time (min)
1	10	0.47	0	47	7.2	40
2	12	0.56	0	25	6.8	46
3	7	0.36	+	5	3.2	85
4	10	0.48	0	14	3.3	60
5	15	0.64	+	14	2.4	90
6	8	0.38	0	13	1.0	25
7	54	1.61	0	5	1.0	90
8	53	1.61	0	2	1.0	100
9	40	1.36	0	4	0.8	120
10	64	1.75	0	3	1.0	90

BSA = body surface area; CHF = congestive heart failure.

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there was evidence of lidocaine toxicity. Both patients were extremely lethargic for multiple hours after catheterization.

The reason for the elevated serum lidocaine levels is related to the increased need for subcutaneous lidocaine in these 2 children. With the advent of earlier and more aggressive interventional and therapeutic procedures, the potential for access problems (inferior vena cava or femoral vessel obstruction, or both) in children with congenital heart disease needs to be appreciated. In addition, the ability of the physician to distinguish between adequate anesthesia and patient anxiety is often difficult in this pediatric age group. Consequently, the use of lidocaine may not be the appropriate form of analgesia. For children in whom difficulties with access become apparent or to whom large doses of subcutaneous lidocaine are administered, alternate forms of sedation or anesthesia (e.g., midazolam hydrochloride, bupivacaine hydrochloride) should be considered. Of significant concern is the frequent occurrence of congestive liver failure in children with congenital heart disease. Lidocaine is known to metabolize in the liver, and elevated serum lidocaine levels can occur despite correct dosage in this population of children. This appeared to be the cause of an elevated lidocaine level in our patient 3.

These results indicate that careful use of lidocaine is warranted, especially in small children. We recommend, for infants <1 m^2, a concentration of $\leq 1\%$ solution of lidocaine. In addition, the total dose should not exceed 4.5 mg/kg.[8] In all circumstances, the lowest concentration and the smallest dose that will produce the desired effect should be administered.

In addition, to reduce the risk of lidocaine toxicity, alternate forms of sedation or anesthesia should be considered for high-risk patients. It should also be recognized that, in addition to the known adverse effects after administration of lidocaine, drowsiness may be an early indication of an elevated blood level of the drug, and serum lidocaine levels should be obtained.

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Indexing Repetitive to Single Ventricular Premature Complexes: A New Concept in Acute Drug Testing

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The clinical application of acute drug testing for the treatment of ventricular arrhythmias is limited by epidemiologic, statistical and therapeutic uncertainties. The suppression of ventricular premature complexes (VPCs) is confounded by statistical analyses that require high-grade suppression simply to confirm a true response[1,2] and by the lack of clinical evidence of efficacy with respect to mortality.[3] Repetitive forms of VPCs are generally considered more important than single VPCs,[4] and improved clinical outcome has been associated with the high-grade suppression of repetitive forms in selected high-risk subgroups.[5] However, the spontaneous variability of repetitive forms is frequently even more marked than single VPCs, rendering statistical analysis nearly impossible.[6] Although these uncertainties have directed attention to the suppression of sustained and nonsustained ventricular tachycardia, both in drug development and therapies, there remains a clinical need to test acutely the efficacy of antiarrhythmic drugs against manifest ventricular arrhythmias. We report a new approach to this evaluation.

Because neither single nor repetitive VPCs have stable frequencies, we tested the hypothesis that a relation between the frequency of single and repetitive forms exists and that such a relation will permit indexing one to the other. Twenty-five 24-hour ambulatory recordings were reviewed (Heart Screen II, Del Mar Avionics, Irvine, California, or Oxford Medilog 4000, Oxford Medical Inc., Clearwater, Florida) without respect to diagnosis or treatment. Inclusion required the presence of single VPCs and repetitive forms for >12 of the 24 hours. The mean and standard deviation (SD) of single VPCs was 207 ± 170 complexes per hour and of repetitive VPCs was 80 ± 114 complexes per hour. The correlation of single VPCs to repetitive VPCs was determined. A significant correlation ($p < 0.05$) between single and repetitive VPCs was observed on 19 of 25 ambulatory tapes ($r = 0.75 \pm 0.15$). In these 19 patients, the frequency of repetitive VPCs was indexed to the frequency of single VPCs with the ratio: ln (repetitive VPCs + 1)/ln (single VPCs

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This study was supported in part by Grant HL28130 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland. Manuscript received September 4, 1990, and accepted November 17, 1990.

+ 1). This repetitive form index was less variable (defined as SD/mean) at 0.62 ± 0.31 than the frequency of single VPCs (0.76 ± 0.42) or repetitive VPCs (1.75 ± 0.92). No patient had the total "spontaneous" disappearance of repetitive VPCs for 2 consecutive hours from 8 A.M. to 4 P.M.; but, despite high-grade ectopy during the daytime hours, repetitive forms often disappeared for several hours at night. Therefore, VPCs were studied from 8 A.M. to 4 P.M. to minimize the effects of spontaneous changes, and VPC frequencies were quantitated in 2-hour time blocks in order to "average out" zeros.

Next, the ambulatory recordings of 10 control patients were prospectively reviewed to establish the stability of the repetitive form index. Each patient had ischemic cardiac disease, and the occurrence of both single and repetitive VPCs for 12 of 24 hours (baseline rate 331 ± 200 single VPCs/hour and 90 ± 86 repetitive VPCs/hour, respectively). No patient had active ischemia or heart failure at the time of the recording. The repetitive form index was computed for four 2-hour blocks, beginning at 8 A.M. The mean baseline repetitive form index for the group averaged 0.73 ± 0.19, and showed remarkable stability (Figure 1). By comparing the repetitive form index of each 2-hour block to the preceding 2-hour block in each of the 10 patients, a spontaneous decrease (12 ± 13%) in the repetitive form index was noted in 12 of 30 comparisons, whereas a spontaneous increase (28 ± 67%) in the repetitive form index was noted in 18 of 30 comparisons. These figures suggest that a decrease in the repetitive form index of 37% (mean decrease − 1.96 SD) or an increase of 162% (mean increase + 1.96 SD) would be significant.

To test the validity of the repetitive form index in an acute drug testing model, 19 patients with documented single and repetitive VPCs received procainamide (939 ± 111 mg), infused, intravenously, at a rate of 25 mg/min. Hourly, single and repetitive VPC frequencies were analyzed from full disclosure monitoring 2 hours before and 6 hours after the drug infusion period. For the group, the repetitive form index was significantly reduced in the first 2 hours after the infusion (0.18 ± 0.26), compared with the 2-hour pretreatment repetitive form index (0.59 ± 0.18; $p < 0.001$). In the overall patient group, a conventional ≥70% reduction in single VPCs had a predictive accuracy of 74%, for a ≥90% reduction in repetitive VPCs, whereas a ≥37% reduction in the repetitive form index had an 89% predictive accuracy, for a ≥90% reduction in repetitive VPCs. The percent change in the repetitive form index paralleled the percent change in repetitive VPCs ($r = 0.88$, $p < 0.01$) much more closely than the percent change in single VPCs ($r = 0.40$, $p > 0.05$). A positive response (defined as a reduction in the repetitive form index by ≥37%) was noted in 14 patients (Figure 1). This positive response was associated with a 98 ± 5% reduction in repetitive VPCs but with only a 68 ± 37% reduction in single VPCs.

Although current studies emphasize mortality, sustained ventricular tachycardia and, to a lesser extent, nonsustained ventricular tachycardia as appropriate end points for therapy, most studies, by tradition and necessity, frequently focus on the antiarrhythmic effects of drugs on simple and intermediate forms of manifest ventricular arrhythmias. The repetitive form index was conceptualized to bypass the limitations of quantitative VPC suppression, and to test its validity as a more stable antiarrhythmic parameter. The repetitive form index was shown to respond to drug intervention in a manner consistent with known antiarrhythmic drug effects. Based on these data, the repetitive form index provides a mathematic construct that has the advantages of: (1) stability, (2) ease of calculation, (3) the potential for automation, (4) close correlation with repetitive form suppression, and (5) the weighting of repetitive events according to the number of VPCs in the run. The repetitive form index takes into account the easier suppression of repetitive than single VPCs,[7,8] and emphasizes residual repetitive forms, even when there is high-grade suppression of single forms. It therefore (1) identifies patients with significant residual repetitive forms after treatment; (2) may serve as a guide away from drug toxicity, because quantitative single VPC suppression, which requires higher drug concentrations for suppression, is not the primary goal of therapy; and (3) may avoid the exclusion of potentially useful drugs that affect repetitive forms significantly while having a less consistent suppressant effect on single forms.

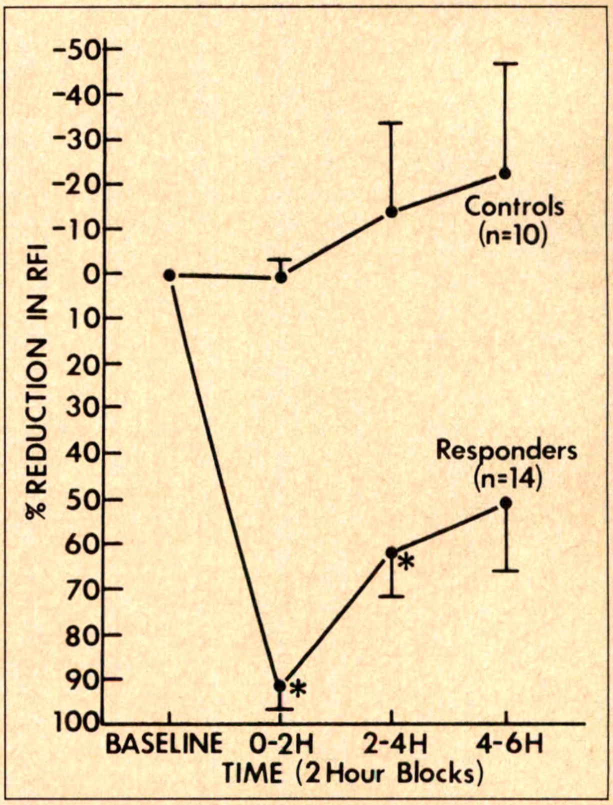

FIGURE 1. Percent reduction in the repetitive form index (RFI) calculated as ln (repetitive ventricular premature complexes + 1)/ln (single ventricular premature complexes + 1) is plotted (mean ± standard error) for 10 control patients and 14 patients who responded significantly to procainamide (repetitive form index decrease of ≥37%). Compared with baseline values, there is a significant reduction (*$p < 0.001$) of the repetitive form index at 0 to 2 and at 2 to 4 hours after drug infusion.

The major limitation of the repetitive form index at this point is the lack of validation against end points such as sustained ventricular tachycardia or mortality. Nonetheless, when the goal is suppression of VPCs, either within the context of antiarrhythmic drug development or clinical therapies, an approach that emphasizes repetitive forms and that deemphasizes single VPCs, such as the repetitive form index, offers a rational approach to the problem.

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Accuracy of Cross-Sectional Echocardiography in Diagnosis of Aortopulmonary Window

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The first echocardiographic descriptions of the aortopulmonary window (APW) were case reports.[1,2] These observations were extended by Smallhorn et al,[3] who described appearances of an isolated APW in 4 infants and compared these with appearances in 14 patients with a common arterial trunk and in 6 with a single pulmonary artery originating at the ascending aorta. In these reports,[1-3] diagnosis was also established by invasive investigation and did not include any patient who had APW with associated cardiac abnormalities. The publication of case reports as late as 1988 suggests that the echocardiographic diagnosis of even an isolated APW is not always straightforward,[4] perhaps because the lesion may be confused with other structural abnormalities.[5] There have been no reports of the accuracy of cross-sectional echocardiography for the prospective diagnosis of APW. We reviewed our experience since the cases previously described[3] to determine the implications for clinical practice.

Review of clinical, echocardiographic, catheterization, surgical and autopsy records between January 1982 and June 1990 revealed 15 patients with APW. Age at presentation ranged from 1 day to 2 years (median 3 months), but all except 1 patient were aged ≤7 months and 6 were neonates. All echocardiographic studies had been performed or reviewed by a physician experienced in this technique. The patients were divided into 2 groups according to whether the APW was an isolated lesion (7 patients) or associated with other congenital heart defects (8 patients). The presenting symptom was cyanosis in 1 patient and cardiac failure or failure to thrive, or both, in the others. During the same period, 3,911 operations for congenital heart defects and 23,803 echocardiographic studies were performed. Also, 50 children with a common arterial trunk and 11 with a single pulmonary artery originating at the ascending aorta were seen.

Seven patients had an isolated APW. One patient was diagnosed at the referring hospital by cardiac catheterization, with echocardiographic confirmation after transfer. Five had the correct diagnosis established by the first echocardiographic examination. The remaining patient had cri du chat syndrome and was referred on the first day of life with cyanosis and hypercarbia "to exclude congenital heart disease." Persistent pulmonary hypertension of the newborn was diagnosed. The echocardiogram was thought to show a structurally normal heart. This patient was next referred at age 5 months because of poor feeding and failure to thrive. The APW was identified on the echocardiogram on this occasion. Nonblinded review of the original study revealed that the lesion had been imaged but overlooked.

Of the 8 patients with associated cardiac anomalies, the APW was diagnosed on the first echocardiographic examination in only 3, 2 of whom had tetralogy of Fallot (1 with right aortic arch) and the third had interruption of the aortic arch distal to the left carotid artery. In 2 patients, the APW was diagnosed on the second echocardiogram. One had an inadequate initial study because of restlessness. Subsequent echocardiography, performed with the infant sedated, revealed the APW in addition to a right aortic arch. Isolated coarctation of the aorta was initially diagnosed in a neonate with heart failure who then underwent repair of that lesion. Postoperative progress was slow despite easily palpable femoral pulses. The echocardiogram was repeated while the patient was receiving full ventilatory support and the APW was diagnosed. In 3 patients, the APW was first diag-

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Manuscript received October 16, 1990; revised manuscript received and accepted November 14, 1990.

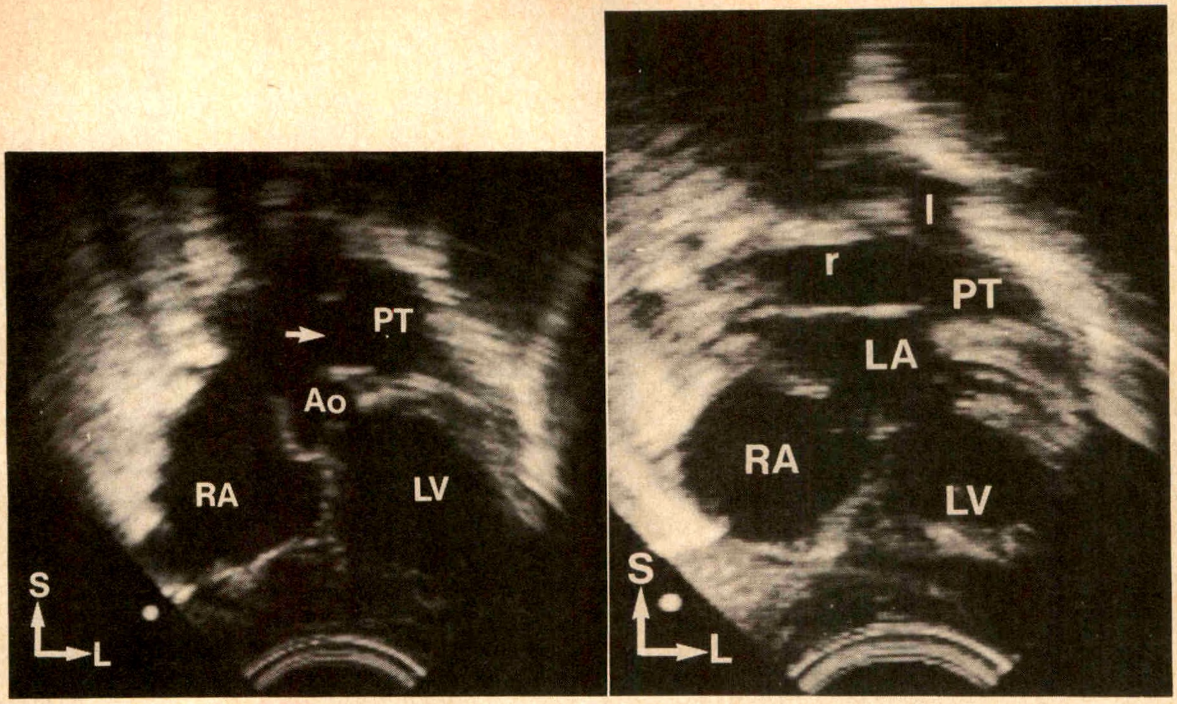

FIGURE 1. ***Left*****, subcostal paracoronal scan through the level of the proximal great arteries showing the aortopulmonary window *(arrow)*. *Right*, scan plane just posterior to that in the *left panel* in the same patient, showing the right pulmonary artery (r) originating from the pulmonary trunk (PT). Ao = aorta; L = left; LV = left ventricle; RA = right atrium; S = superior.**

nosed at cardiac catheterization. All had ventricular septal defects, with additional aortic valve stenosis in 1. Nonblinded review of the initial echocardiograms demonstrated the APW, which had been overlooked in each case. There was no false positive diagnosis of APW.

Subcostal paracoronal scanning planes through the pulmonary trunk were the views that most reliably allowed recognition of the echo-free communication with the adjacent ascending aorta (Figure 1, left panel). Separate identification of the right pulmonary artery as it passed posterior to the ascending aorta was obtained by tilting the scanning plane slightly posterior to this plane

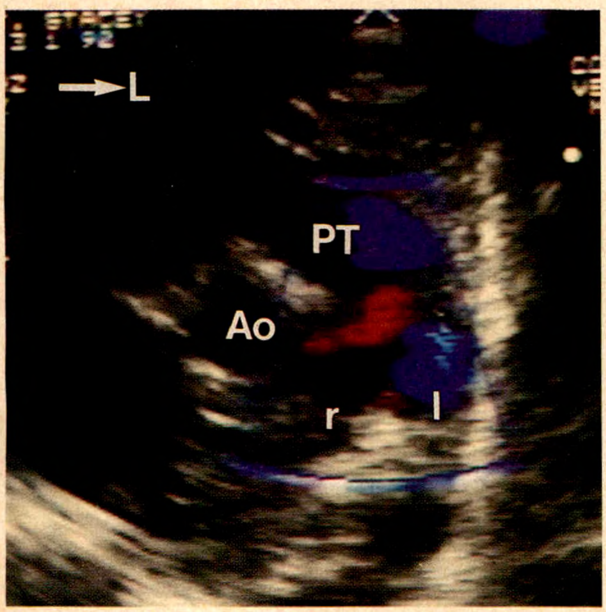

FIGURE 2. Parasternal short-axis scan cephalad to the aortic valve showing the aortopulmonary window with superimposed Doppler color-flow map revealing laminar flow (coded red flowing toward the transducer) from the aorta (Ao) to the pulmonary trunk (PT) in systole, together with "normal" forward flow in the pulmonary trunk (coded blue, flowing away from the transducer). l = left pulmonary artery; other abbreviations as in Figure 1.

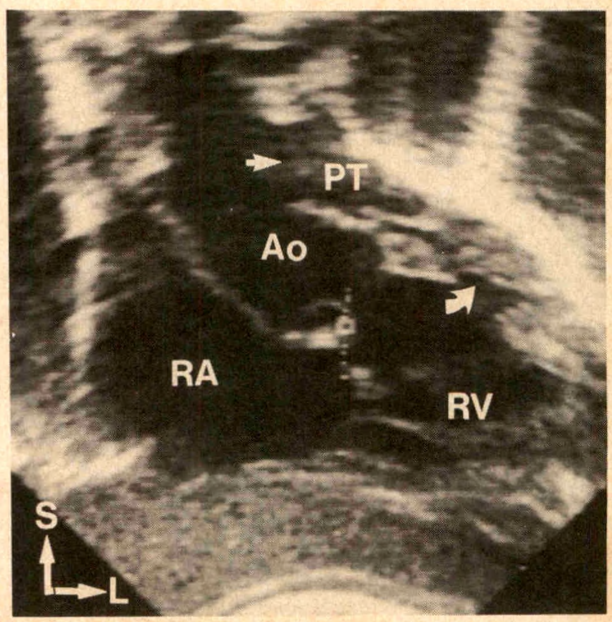

FIGURE 3. Subcostal paracoronal scan through the level of the proximal great arteries showing an aortopulmonary window *(straight arrow)* associated with tetralogy of Fallot. Note the narrow right ventricular outflow tract *(curved arrow)* and the large ascending aorta (compare Figure 1, left panel). RV = right ventricle; other abbreviations as in Figure 1.

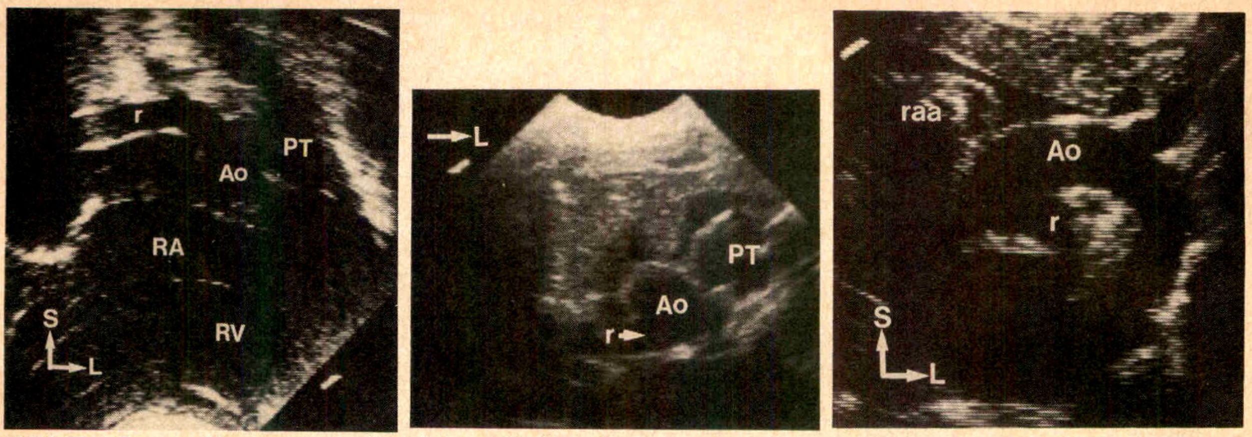

FIGURE 4. Comparable appearances in an infant with the right pulmonary artery originating from the aorta (Ao) as an isolated abnormality. *Left*, subcostal paracoronal plane; *middle*, parasternal short-axis plane; *right*, suprasternal view in the long axis of the ascending aorta. See text for discussion. raa = right atrial appendage. Other abbreviations as in Figures 1 and 3.

(Figure 1, right panel). The APW could be confirmed from a parasternal short-axis plane cephalad to the aortic valve (Figure 2).

Surgery was not performed in 2 patients. In view of the poor overall prognosis, the child with cri du chat syndrome was not treated surgically, and died at the age of 6 months. One other infant with an undiagnosed dysmorphic syndrome and multiple extracardiac abnormalities died at 15 days without surgery. Surgical repair was performed in the remaining 13 patients. Two infants died at surgery, at ages 6 weeks and 2 days, respectively. Both were moribund when first seen. The correct diagnosis was established by echocardiography at presentation in both, obviating the need for cardiac catheterization. One of these had an isolated APW, whereas the other also had interruption of the aortic arch. There have been no late deaths among the 11 survivors of surgical repair during follow-up of 1 month to 7 years (median 3.5 years) since operation.

APW is a rare lesion, occurring in about 0.2% of patients with congenital heart defects,[6] and was present in only 15 of 3,911 patients (0.4%) undergoing surgery for congenital heart defects in our unit during the course of this study. The ability to diagnose an isolated APW by cross-sectional echocardiography has been recognized for several years,[1-3] but the accuracy of the technique for diagnosis, whether it exists as an isolated abnormality or is associated with other congenital heart defects, is unknown.[4] There were no patients with APW in a prospective study of the accuracy of echocardiography in the diagnosis of congenital heart disease in 126 infants and children.[7]

Our data indicate that cross-sectional echocardiography is reliable for the detection of isolated APW. Our inability to make the diagnosis reliably from the initial echocardiogram when there were major associated congenital heart defects was disappointing. Retrospective review demonstrated the APW in 5 of 6 patients in whom it had been "missed" in the initial echocardiographic report. In the remaining patient, the initial study was technically inadequate, and diagnostic images were obtained when the study was repeated with the infant sedated. This suggests that the lesion was not diagnosed because the operator did not think of the possibility of the presence of the lesion rather than because of inability to obtain adequate images.

Importantly, as the lesion is often described as an abnormality that occurs in isolation,[1-4] 8 of our 15 patients with APW had associated congenital heart defects. However, a similar incidence and spectrum of associated abnormalities have been documented in a pathology series.[6] The inclusion in this series of 2 infants with tetralogy of Fallot (Figure 3) and the previous description of 3 other patients with APW, pulmonary atresia and ventricular septal defect,[8] indicates that the recognition of a "normal right ventricular outflow tract and pulmonary valve"[2] is not a criterion for diagnosis.

Suprasternal long-axis cuts of the aorta were advocated to demonstrate the communication between the ascending aorta and the pulmonary trunk in patients with APW.[3] However, no patients with the isolated abnormality of the right pulmonary artery arising from the ascending aorta were included in that report,[3] and we believe that the previously described subcostal and parasternal cuts (Figures 1 and 2) are more reliable in the differentiation of an APW from that lesion (Figure 4).[5] Visualization of the aortopulmonary septum in ≥ 2 planes and the presence of a "T" artifact at the margins of an APW should eliminate the difficulty of echo "dropout" in the region of crossover of the ascending aorta and pulmonary trunk. The origins of the coronary arteries should also be identified.[9] Doppler color-flow mapping was helpful in confirming the diagnosis in the 2 patients seen since this technique became available (Figure 2) when used in a manner similar to that reported in a previous case report.[4] This technique may facilitate a more reliable echocardiographic diagnosis of APW in the future. Conventional pulsed- and continuous-wave Doppler at the site of the APW may not be helpful, because the communication is large and nonrestrictive. However, retrograde diastolic flow in the aortic arch, or forward diastolic flow in the pulmonary trunk distal to the window, may be useful

ancillary evidence of left-to-right shunting in diastole via the APW.

Our experience indicates that APW can and should be diagnosed by cross-sectional echocardiography. However, accurate diagnosis requires exclusion of this lesion in any patient with a ventricular septal defect or an abnormality of the aortic arch.

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Frequency of Occurrence of Residual Ductal Flow After Surgical Ligation by Color-Flow Mapping

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Whereas closure of patent ductus arteriosus (PDA) with large left-to-right shunts may be required for symptomatic relief, the reason for recommending closure of small ducts is to prevent infectious arteritis, otherwise reported with an incidence of 0.45% per year.[1] Ductal division usually offers complete closure, whereas ligation has been reported to be associated with recurrences, either due to recanalization or to incomplete closure.[2–6] The true incidence of residual ductal shunting after PDA ligation has not been clearly defined, because follow-up generally has been based on auscultatory findings that have proved unreliable in identifying residual ductal shunting.[7] Because incomplete PDA ligation may necessitate reoperation or life-long infection prophylaxis, it is important to identify patients with small residual ductal flow. Color-flow mapping is a very sensitive method for the identification of PDA flow.[7–9] Consequently, color Doppler studies were performed in 31 patients who had undergone surgical PDA ligation to evaluate the incidence of residual ductal flow.

Thirty-one consecutive patients undergoing PDA ligation from January 1, 1987, to December 31, 1989, were examined. The median age at surgery was 14 months (range 5 weeks to 27 years). All except 1 patient were <14 years of age. The time from surgery to follow-up ranged from 1 to 13 months (median 4). PDA was an isolated finding in 17 patients, whereas 14 had associated cardiac lesions: ventricular septal defect ($n = 4$), atrial septal defect ($n = 2$), atrioventricular septal defect ($n = 2$), atrial and ventricular septal defects ($n = 1$), aortic coarctation ($n = 3$), mitral prolapse ($n = 1$) and pulmonary stenosis ($n = 1$). Nine patients were referred to surgery after cardiac catheterization, and 22 were referred after only echocardiography.

Isolated PDA ligations were performed through a left lateral thoracotomy ($n = 28$) or a sternotomy ($n = 3$) if PDA ligation was part of a total correction. All PDAs were intraoperatively judged appropriate for duct ligation. In 24 patients ligation was performed with silk ligatures, whereas a Hemoclip® was used in 7 patients. The ductal thrill disappeared completely in all patients.

Echocardiographic examinations were performed with a Toshiba SSH-160 or SSH-65A. Standard projections were used to search for any residual ductal flow. Guided by the color-flow map, spectral velocity tracings of the PDA flows were obtained with pulsed and continuous-wave Doppler. Great care was taken to confirm PDA flow and to eliminate other sources of disturbed flows in the pulmonary trunk.

No clinical evidence (i.e., continuous murmur) of residual PDA flow was identified in any of the patients. However, in 7 of 31 patients, color-flow mapping revealed typical ductal flow into the main pulmonary artery. Pulsed and continuous-wave Doppler corroborated the color-flow finding in all cases. Maximal flow velocity exceeded 3.5 m/s in all but 1 patient, whereas low velocities (<2.0 m/s) only were found in 1. Based on echocardiographic flow volumetry, residual Qp:Qs was <1.3 in all cases. In no subject was there evidence of other cardiac lesions that might mimic residual PDA flow, nor was there any brief transient retrograde flow at the inferior aspect of the main pulmonary artery, which may be a normal finding.[7] No association between age at surgery, surgical technique, follow-up interval, ductal size or additional cardiac lesions, and residual shunting could be identified.

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Manuscript received October 22, 1990; revised manuscript received and accepted November 26, 1990.

The true incidence of residual shunting after PDA ligation is not known. Although several early studies reported data on the recurrence rate, the methods used to detect residual shunting and to discriminate between "incomplete closure and recanalization" were not clearly defined. However, clinical findings (persistent murmur) probably were of major importance. Bickford[2] reported failure of complete PDA ligation in 4% (5 in 120 cases), but pointed out that ligation was incorrectly performed in medium-sized ducts. Trusler[3] found that 1% of ligated ducts "recanalized." Panagopoulos et al[4] reported recanalization or incomplete closure in 4 of 963 PDA ligations (0.4%), whereas Jones[5] noted recanalization or incomplete closure in 12 of 61 patients (20%). In patients >50 years of age undergoing PDA ligation, Ng et al[6] had 2 clinical recurrences in 7 ligations, including 1 calcified duct.

Despite the use of standard surgical procedures and complete disappearance of the ductal thrill after ligation, 7 of the 31 patients (23%) in our study had color Doppler echocardiographic evidence of residual ductal flow not evident clinically. Because of the low sensitivity of physical findings in identifying trivial residual PDA shunts, the surgical success rate previously reported may well have been overestimated.

In the only previous study on the use of color-flow mapping to identify residual PDA flow, Musewe et al[7] found 2 of 30 children (6%) to have residual ductal shunting after duct ligation. The cause for the difference in the incidence of residual PDA flow between that study and our patients is unknown. In our study, shunting was not confined to patients studied in the first postoperative months. However, the median time from duct ligation to Doppler assessment in our patients was 4 months, whereas in the study of Musewes et al the mean interval between surgery and restudy was much longer (44 ± 58 months). Consequently, late spontaneous closure of residual ductal patency, as has been observed after transcatheter duct occlusion, cannot be excluded and may contribute to the difference in incidence of residual flow seen.

No obvious trend for incomplete occlusion occurred in the patients with large-sized PDAs. After dissection of the PDA, the surgeon in each case made his decision whether to ligate or divide the PDA. In all subjects, ligation was considered appropriate. The surgical procedure was performed in accordance with basic principles and the complete disappearance of the PDA thrill suggested ligation to be a satisfactory procedure.

During the echocardiographic examination, care was taken to eliminate other reasons for flow changes in the main pulmonary artery as well as in adjacent structures, such as the left coronary artery. Bearing these possibilities in mind, recently published studies appear to confirm the accuracy of Doppler color-flow imaging for identifying ductal patency.[7-9]

The clinical relevance of residual ductal flow detected by color Doppler examination (which is clinically silent) is unknown. Color Doppler interrogation will detect regurgitation of most tricuspid, pulmonary and mitral valves in normal adults. Antibiotic prophylaxis against infective endocarditis, at times of potential bacteremia, would not normally be recommended for such patients. Moreover, the risk of endarteritis in patients with hemodynamically insignificant PDAs is probably much less than the risk of 0.45% per year reported for all ducts[1] from an era of early antibiotic availability and poor dental hygiene.

Nevertheless, if our data are confirmed in larger series, changing the operative procedure toward duct division may be advisable, unless future catheter techniques change the treatment strategy. The recently published data on this technique have so far been promising[7,10,11] and the closure rate reported higher than the one obtained by ligation in our series. If residual shunting is caused by incomplete ligation, an alternative approach would be to perform intraoperative color-flow mapping, with the option of either placing another ligature or dividing the PDA should residual ductal flow be identified.

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Electrocardiographic, Enzymatic and Echocardiographic Evidence of Myocardial Damage After Tityus Serrulatus Scorpion Poisoning

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The cardiovascular manifestations after a Tityus serrulatus scorpion sting consist of arterial hypertension or hypotension, heart failure, pulmonary edema, shock and electrocardiographic changes.[1] Pulmonary edema evoked by scorpion toxin has been attributed to left ventricular failure induced by the venom or to increased pulmonary vascular permeability produced by vasoactive substances that might be released by the venom.[2] The demonstration of myocardial damage and depressed left ventricular systolic function in patients with pulmonary edema following scorpion sting could support the hypothesis that this severe complication is cardiogenic in origin. This report describes results of electrocardiographic, enzymatic and echocardiographic studies in 5 patients with severe envenomation after a Tityus serrulatus scorpion sting.

Five children, aged 3 to 9 years, with severe envenomation after scorpion sting were admitted to the intensive care unit of Hospital das Clínicas, Federal University of Minas Gerais, from August to December 1989. The scorpions were examined and identified as Tityus serrulatus. On admission, chest x-ray and electrocardiograms were recorded and repeated whenever necessary. Blood samples were drawn for biochemical and hematologic testing. M-mode, 2-dimensional and color Doppler echocardiographic examinations (Siemens Sonoline CF) were performed during the patients' stay in the intensive care unit and repeated after discharge from the hospital when they returned for follow-up.

Treatment consisted of intravenous administration of scorpion antivenom in amounts sufficient to neutralize 12 mg of venom (scorpion antivenom, FUNED, Minas Gerais, Brazil), and continuous evaluation and electrocardiographic monitoring. Pain at site of the sting and vomiting were treated with intravenous administration of dipirone (40 to 80 mg/kg/day) and metoclopramide (0.5 to 1.0 mg/kg/day), respectively. Pulmonary edema was treated with oxygen, diuretics and digitalis.

The clinical data of the patients on admission to the intensive care unit are listed in Table I. Electrocardiographic changes are listed in Table II. All children had sinus tachycardia. Patients 3, 4 and 5 had an acute myocardial infarction-like pattern lasting 24 hours in

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TABLE I Clinical Data in Five Patients Stung by Tityus Serrulatus

Clinical Data	Patient Number 1	2	3	4	5
Age (year) & sex	9/M	9/M	4/F	3/M	3/F
Time between sting and antivenom administration (h)	5	13	0.5	1	2
Time between sting and admission to ICU (hours)	32	14	24	9	2
Pain at site of sting	+	+	+	+	+
Vomiting	+	+	+	+	+
Hyperthermia	0	+	0	0	+
Restlessness	+	+	+	0	0
Prostration	+	+	+	0	+
Diaphoresis	0	0	+	+	+
Tachypnea	+	+	+	+	+
Tachycardia	+	+	+	+	+
Arterial hypertension	0	0	0	0	0
Pulmonary edema	+	+	+	0	0
Outcome	Alive	Alive	Alive	Alive	Alive

ICU = intensive care unit; + = present; 0 = absent.

TABLE II Laboratory Data in Five Patients Stung by Tityus Serrulatus

Pt. No.	ECG	CK (10–80 U/liter)	CK-MB (10 U/liter)	PE on Chest X-Ray	Leukocytes (5,000–(10,000 mm^3)	Blood Glucose (70–110 mg/dl)	Serum Amylase (60–160 U/dl)
1	Sinus tachycardia	120	—	+	25,300	175	15
2	Sinus tachycardia VPC	20	—	+	20,600	125	140
3	Sinus tachycardia MI–like pattern	64	16.5	+	12,900	82	162
4	Sinus tachycardia MI–like pattern	76	—	0	31,600	205	292
5	Sinus tachycardia MI–like pattern	213	38	0	31,980	246	364

CK = creatine kinase enzyme; CK-MB = creatine kinase isoenzyme MB; ECG = electrocardiogram; MI = myocardial infarction; PE = pulmonary edema; VPC = ventricular premature complex; 0 = absent; + = present; – = not measured.

TABLE III Echocardiographic Data in Five Patients Stung by Tityus Serrulatus

Pt. No.	Time Between Sting and Echo Examination	HR (beats/min)	LVDd (mm)	LVDs (mm)	FS (%) (29–45%)	MR
1	3 Days	105	43	35	18	0
	20 Days	78	45	29	36	0
2	21 Hours	145	42	39	7	+
	13 Days	76	34	21	38	0
3	2 Days	140	36	30	17	0
4	19 Hours	171	31	24	23	+
	8 Days	112	29	16	45	0
5	9 Hours	154	36	27	25	+
	10 Days	115	31	22	29	0

Echo = echocardiographic; FS = left ventricular fractional shortening; HR = heart rate; LVDd = left ventricular internal dimension at end-diastole; LVDs = left ventricular internal dimension at end-systole; MR = mitral regurgitation; 0 = absent; + = present.

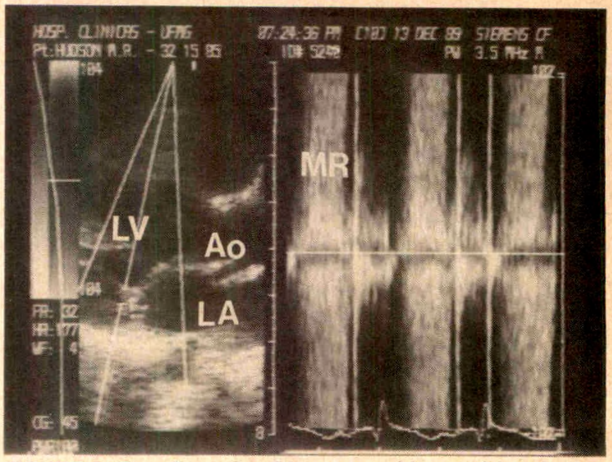

FIGURE 1. Two-dimensional (parasternal long-axis), pulsed Doppler and color-flow mapping examination performed in patient 4 nineteen hours after scorpion sting showing mitral regurgitation. Ao = aorta; LA = left atrium; LV = left ventricle; MR = mitral regurgitation.

patient 3 and 2 days in patients 4 and 5. Patient 2 had frequent ventricular premature beats with periods of bigeminy. These changes lasted 48 hours.

Laboratory data are listed in Table II. A mild increase in creatine kinase enzyme activity was detected in patients 1 and 5, the latter having an electrocardiogram resembling an acute myocardial infarction–like pattern. The other 2 patients with this electrocardiographic change had normal creatine kinase activity, determined 48 hours after the sting in patients 3 and 9, and 30 hours after the sting in patient 4. Creatine kinase isoenzyme MB was measured 24 hours after the sting in patients 3 and 5 and both showed mildly increased activity. In addition to hypoxemia, patients 1, 2 and 3 had radiologic evidence of pulmonary edema. None of them needed mechanical ventilation. All patients had leukocytosis; hyperglycemia was detected in all patients except in patient 3. Increased serum amylase activity was present in patients 3, 4 and 5.

Echocardiographic changes are listed in Table III. Examinations performed in all patients from 9 hours to 3 days after the scorpion sting showed depressed left ventricular systolic function characterized by poor motion of the interventricular septum or decreased motion of the left ventricular posterior wall and decreased left ventricular fractional shortening, or a combination of these. Color-flow Doppler mapping studies showed mitral regurgitation in patients 2, 4 and 5 (Figure 1). Follow-up was not possible in patient 3. Examinations performed at times ranging from 8 to 20 days after the sting showed improvement of left ventricular systolic function in all patients (Figure 2) and disappearance of mitral regurgitation.

This study shows that reversible depressed left ventricular systolic function and mitral regurgitation assessed by means of echocardiography can occur in patients with systemic manifestations after Tityus serrulatus scorpion sting. The pathogenesis of depressed left ventricular systolic function is not yet known. It could result from acute arterial hypertension[2] or from myocardial damage due to an effect of massive catecholamine

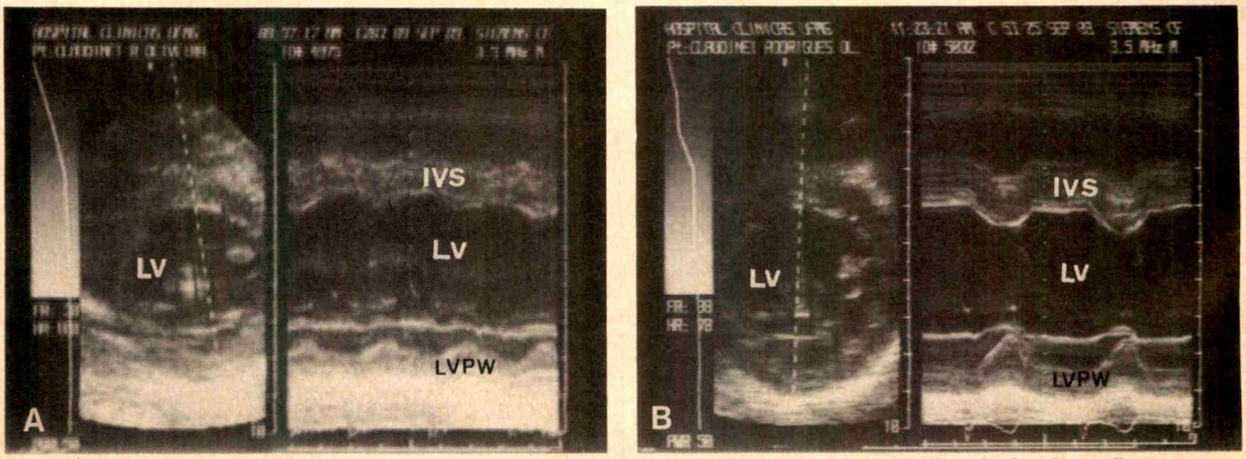

FIGURE 2. M-mode and 2-dimensional (parasternal short-axis) echocardiograms recorded in patient 1. *A*, echocardiogram recorded 3 days after scorpion sting showing hypokinesia of interventricular septum and left ventricular posterior wall. *B*, echocardiogram recorded 20 days after sting showing improvement of interventricular septum and left ventricular posterior wall motility. IVS = interventricular septum; LV = left ventricle; LVPW = left ventricular posterior wall.

release as in pheochromocytoma, or due to a direct effect of the venom.[3,4] Histologic studies performed in fatal cases of scorpionism have shown degenerative changes, focal necrosis, interstitial edema and hypercellularity mainly involving the papillary muscles and the subendocardium.[5,6] Increased creatine kinase enzyme activity has been observed in patients with severe scorpionism who have electrocardiographic changes resembling an acute myocardial infarction–like pattern.[7] These electrocardiographic changes or increased creatine kinase enzyme activity, or both, were also detected in our patients and are evidence of myocardial damage. However, our data do not permit a conclusion as to whether the myocardial damage was caused directly by the venom or by an effect of massive catecholamine release.

Transient acute mitral regurgitation was observed in 3 patients. It may have resulted from impaired contraction of papillary muscles or from alteration of geometry and functional integrity of the mitral valve apparatus secondary to left ventricular dysfunction, or both.

The echocardiographic findings support the hypothesis that acute left ventricular failure is one of the pathogenic mechanisms of pulmonary edema after scorpion envenomation. Previous experimental and clinical studies provide evidence of left ventricular dysfunction associated with pulmonary edema evoked by scorpion venom. Hemodynamic measurements in dogs have shown decreased compliance with impairment of left ventricular filling and emptying, and elevated systemic and pulmonary pressures.[8] Pulmonary hypertension and increased pulmonary capillary wedge pressure were also observed in 2 patients with pulmonary edema after a scorpion sting.[7] A reversible pattern of dilated cardiomyopathy was also detected by means of echocardiography in a 7-year-old girl with pulmonary edema after a scorpion sting.[9] However, pulmonary edema could also result from isolated or associated increased pulmonary vascular permeability produced by vasoactive substances that might be released by the venom.[2]

In our series, echocardiography was more sensitive than electrocardiography or creatine kinase enzyme assays in assessing myocardial compromise after a scorpion sting. Echocardiographic examinations should be performed in patients with severe scorpionism, because detection of depressed left ventricular systolic function could result in improved management and further reduction in mortality.

Acknowledgment: We are grateful to the medical and nursing staff of the intensive care unit, Hospital das Clínicas, Federal University of Minas Gerais, who participated in the treatment of the patients. We particularly thank Simonnete A. Torres, MD, and Andrea Charmovickz, MD.

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Creation of Pseudo Narrowing During Coronary Angioplasty

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Since the initial description of percutaneous transluminal coronary angioplasty (PTCA) by Gruentzig et al,[1] the application of PTCA has expanded dramatically, exceeding 300,000 cases annually. Along with this growth, patients with increasingly complex coronary arterial anatomy and lesions are being treated. Technologic advances, coupled with operator experience, have reduced acute procedural risk to an acceptable, although not negligible, level.[2] During the performance of PTCA, the interventional cardiologist must quickly recognize and appropriately manage any complication that arises. In addition, the operator must be able to differentiate true complications from pseudocomplications; that is, the operator must recognize the artifactual nature of an apparent complication that is not necessarily what it appears to be. For instance, Espluges et al[3] reported the appearance of persistent staining by contrast material of the arterial wall, suggesting significant dissection during PTCA while using a new monorail balloon catheter. The artifact disappeared with balloon deflation.[3] We report a patient in whom straightening of a tortuous coronary artery by a PTCA guidewire created the false impression of 2 new narrowings during PTCA.

A 65-year-old man, who had had an acute myocardial infarction 6 days earlier, had an uncomplicated course and did not receive thrombolytic therapy. Cardiac catheterization revealed 95% narrowing in diameter of a single coronary vessel in a tortuous proximal right corory artery (Figure 1). PTCA was performed by standard technique through the right femoral artery with an 8Fr Judkins right coronary guide catheter (Baxter Healthcare, Santa Anna, California), an 0.018″-guidewire (Hi Torque Floppy™, Advanced Cardiovascular Systems, Santa Clara, California), and a 2.5-mm PTCA balloon catheter (Skinny .018™, SciMed, Maple Grove, Minnesota). The narrowing was crossed without difficulty and dilated to 10 atm for 3 minutes and to 11 atm for 2 minutes. Intracoronary nitroglycerin was given (200 µg) and (with the guidewire still across the lesion) arteriography repeated. In addition to a residual 50% stenosis at the initial narrowing, 2 new narrowings proximal to the target stenosis were now angiographically revealed (Figure 2). The Skinny .018™ PTCA catheter was removed and exchanged for a 3.0-mm Pinkerton™ (Advanced Cardiovascular Systems) PTCA catheter, and the original lesion dilated once again. Administration of additional intracoronary nitroglycerin failed to relieve the new proximal narrowings. A decision was made not to treat the new narrowings with angioplasty but to remove the balloon and guidewire systems instead and assess the results. Arteriography, immediately repeated after removal of the PTCA systems, demonstrated a residual 25% diameter narrowing at the original PTCA site,

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Manuscript received August 14, 1990; revised manuscript received and accepted November 21, 1990.

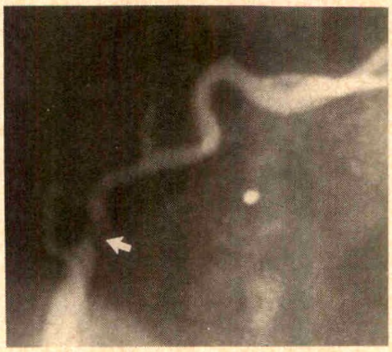

FIGURE 1. Angiogram before angioplasty revealing lesion *(arrow)* in tortuous right coronary artery.

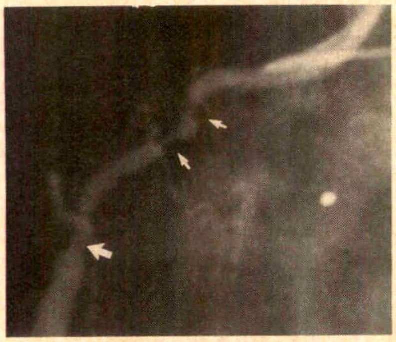

FIGURE 2. Interim angiogram after dilation of the right coronary artery stenosis with a 2.5-mm balloon angioplasty catheter, with the guidewire across the lesion, demonstrating a residual 50% stenosis at the site of the initial dilation *(large arrow)* and the angiographic appearance of 2 new stenoses proximal to the target lesion *(small arrows)*.

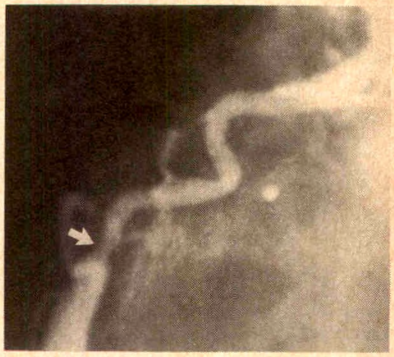

FIGURE 3. Final angiogram after angioplasty demonstrating a 25% residual stenosis at the original angioplasty site *(arrow)* and a normal vessel proximally. The initial target lesion was redilated with a 3.0-mm balloon angioplasty catheter, and the balloon catheter and guidewire removed before this cine sequence.

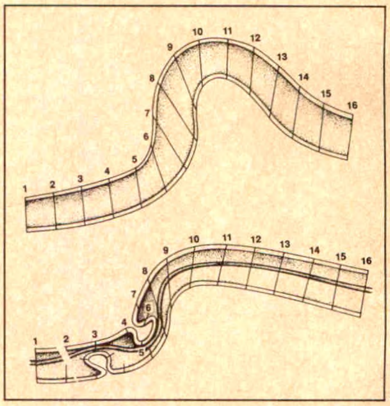

FIGURE 4. Proposed mechanism for creation of pseudo narrowings by straightening of the coronary artery by a coronary guidewire. Because the overall length of the vessel wall must be maintained as the segment is straightened, the wall invaginates at 2 locations to accommodate the extra wall length. See text for details.

with complete resolution of the proximal "narrowings" (Figure 3).

Figure 4 illustrates the proposed mechanism by which pseudo narrowings can be created by the straightening of a coronary artery segment with an angioplasty guidewire. The top portion of Figure 4 shows the tortuous vessel segment before guidewire placement. Numbered lines mark equidistant points along the artery wall. The lower portion of Figure 4 illustrates the effects of vessel straightening. While the ends of the segment of the artery are maintained in a static position, the straightening of the segment by the guidewire causes invagination of the central portion of the vessel at 2 points to accommodate the excess in vessel wall length. The numbered lines in this portion of Figure 4 demonstrate that the overall length of the vessel wall is maintained by the folding of the wall into the 2 invaginations. Removal of the guidewire then allows the vessel to return to its normal tortuous configuration, relaxing the arterial wall, and culminating in resolution of the pseudo narrowings.

A more common cause of new narrowing during PTCA is vasospasm secondary to the endothelial trauma that occurs during manipulation of angioplasty devices. This phenomenon is best managed with intracoronary nitroglycerin, sublingual nitroglycerin, or sublingual nifedipine, or a combination of these, along with removal of the irritant stimulus. In our case, persistence of the new narrowings despite repeated doses of intracoronary nitroglycerin and the temporal relation of PTCA system removal to their disappearance supports arterial wall invagination as the mechanism of narrowing. Review of the 2,150 PTCA procedures performed at our institution over the past 2 years suggests an incidence of pseudo narrowing as frequent as 1 in 250 procedures involving the right coronary artery, with variable compromise of anterograde coronary flow. Unusual iatrogenic pseudocomplications such as those illustrated by this case must be distinguished and managed appropriately. Knowledge of this pseudocomplication will help avoid inappropriate treatment, including unnecessary PTCA that could potentially expose the patient to additional risk.

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Myocardial Ischemia-Induced Transient Anterior Conduction Delay

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Although a trifascicular structure has been proposed for the left bundle branch, conduction delay in a third fascicle is rarely recognized.[1,2] This may be due to a lack of specific features for diagnosis of anterior conduction delay,[3] because identical patterns can be obtained with right ventricular hypertrophy or posterior myocardial infarction.[4] We present the stress test of a patient with critical coronary artery disease that exhibited ischemia and transient, complex conduction delay, manifested as prominent anterior forces followed by right bundle branch block (RBBB), with evolution of anteroseptal infarction.

An active 72-year-old hypertensive man was referred for treadmill testing. Cardiac examination was unremarkable (blood pressure 140/70 mm Hg, heart rate 70 beats/min). The electrocardiogram was normal. By the end of stage I (Bruce protocol), the QRS widened to 105 ms, from 95 at baseline, with R-wave notching inferolaterally. At 4 minutes and 30 seconds, the patient became mildly dyspneic, the PR interval widened from 160 to 190 ms and the QRS to 120 ms, with concomitant ST elevation in V_1 and depression inferolaterally (Figure 1). By the end of stage II (6 minutes), the QRS morphology changed, with the 80-ms axis manifesting marked anterior displacement in the horizontal but no change in the frontal plane. In addition, the small Q waves initially present in leads II and V_6 disappeared. Blood pressure decreased to 88/68 mm Hg, pulse rate increased to 130 beats/min, the patient developed angina, and the test was discontinued. Four seconds into recovery, the QRS duration increased to 160 ms, with widening and rightward-anterior direction of the terminal QRS forces consistent with superimposed RBBB. At 4 minutes, the QRS duration narrowed to 120 ms with rsR's' morphology in V_1 and evidence of transmural injury current in V_1, V_2 and V_3. At 6 minutes and 3 seconds, the QRS duration shortened to 105 ms and the prominent anterior forces abated in V_1; the anterior injury current resolved, but ST depression persisted inferolaterally. At 15 minutes, the electrocardiogram manifested hyperacute anteroseptal infarction. Despite thrombolysis, creatine phosphokinase MB-subunit increased to 54 IU/liter. Angiography, 3 days later, revealed anterior wall hypokinesia, and ostial occlusion of the right coronary artery, which was receiving extensive collateral flow from a proximally and subtotally occluded left anterior descending artery. After revascularization, the patient is in excellent condition.

Exercise-induced ST elevation, in the absence of a myocardial scar, suggests critical coronary artery disease or spasm. Furthermore, transient, ischemia-induced RBBB during stress testing has been observed with, but is not limited to, high-grade

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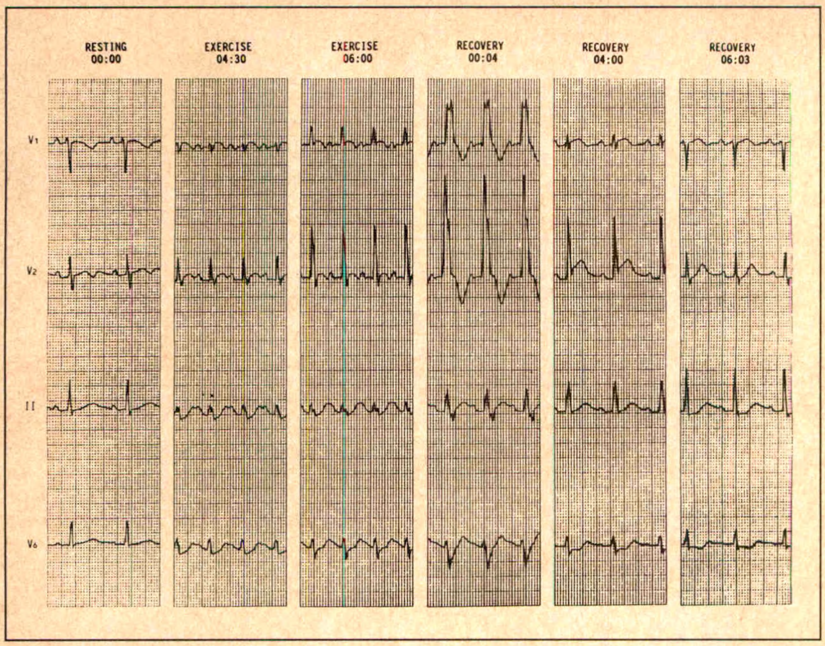

FIGURE 1. Lead segments from a 12-lead electrocardiogram at rest, during stress and recovery.

proximal left anterior descending artery lesions.[5] This report graphically illustrates the masking effect of RBBB, even on severe injury current.

We also noted the development and resolution of a complex conduction delay. After an initial QRS prolongation, prominent anterior forces were manifested and preceded the superimposition of complete RBBB. One plausible explanation for this finding is that anterior conduction delay developed independent of, and simultaneous with, a right conduction delay, which eventually led to complete RBBB. Given the R peak time <50 ms and the absence of r′ or R′ in V_1 or V_2, the QRS morphology in V_1 at 6 minutes does not meet the criteria for diagnosis of incomplete or complete RBBB.[3] Furthermore, the disappearance of the small Q waves, initially present in leads II and V_6, is not seen with RBBB.[2] Finally, although the concurrent PR prolongation may have resulted from conduction disturbance in either the atrioventricular node, the bundle of His or the left bundle branch, it certainly cannot be explained by conduction abnormality in the right bundle branch alone. Thus, the prominent anterior forces observed at 6 minutes may have resulted from anterior conduction delay,[1,2] and the simultaneous QRS widening, which cannot be explained by anterior conduction delay, may be a reflection of evolving right conduction delay. Alternatively, this QRS widening may have arisen from conduction being globally slower, at this point in time, in the left than in the right bundle, with additional delay in the anterior fibers. Kulbertus et al[1] and Reiffel and Bigger[2] attributed intermittent anterior QRS axis shift occurring with atrial premature beats to anterior conduction delay. This defect, defined as anterior QRS axis shift without a change in the frontal plane or significant QRS widening, and without rSr′ in V_1, may result from delay in the fibers to the anterior septum and not necessarily a specific fascicle.[2] Hoffman et al[4] proposed that such delay could also arise from disproportion in the length of several fascicular divisions, with the "anterior" fascicle being the longest. Another, speculative explanation is that these prominent anterior forces were merely the first effect of evolving RBBB.[6] However, the severity of the coronary artery disease was such that the myocardium and conduction system were likely to be globally in jeopardy, thus affording diffuse and extensive conduction abnormalities.

Acknowledgment: We would like to thank Melvin Cheitlin, MD, Myrvin Ellestad, MD, Victor Froelicher, MD, Henri Kulbertus, MD, and Henry Marriott, MD, for their thoughtful comments, and Michael Berbin for technical assistance.

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Endomyocardial Biopsy Finding in Two Patients with Idiopathic Dilated Cardiomyopathy Receiving Long-Term Treatment with Amiodarone

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Amiodarone, a highly effective antiarrhythmic agent, accumulates in different tissues, causing a variety of adverse effects.[1-3] Long-term amiodarone treatment may cause diffuse interstitial pulmonary fibrosis and inflammation, with accumulation of cytoplasmic bodies containing electron-dense lamellas in pneumocytes and alveolar macrophages.[1,2] Similar bodies have been described in liver, lymph nodes, blood leukocytes, cornea, endothelial cells of skin, colonic mucosa,[3] and Schwann cells. Such bodies also have been found in cardiac myocytes of experimental animals treated with multiple doses of this drug[4,5]; however, to our knowledge, they have not been reported in the myocardium of patients treated with amiodarone. This report describes ultrastructural changes in the myocardium of 2 patients with idiopathic dilated cardiomyopathy who had received long-term amiodarone treatment.

Patient 1, a 50-year-old man, was referred for cardiac transplantation. He had been treated chronically with inotropic agents, diuretics and antiarrhythmic agents, for recurrent ventricular arrhythmias, and had received amiodarone for the last 4 years.

Patient 2, a 53-year-old woman, was referred with a history of life-threatening, recurrent ventricular arrhythmias, for which she had been treated with amiodarone for the past 2 years.

Right ventricular endomyocardial biopsies were obtained from each patient for histologic (hematoxylin, eosin and Masson trichrome methods) and electron microscopic (Karnowsky fixation, osmium tetroxide postfixation and Epon-Araldite embedding) studies.

Light microscopic examination of the 2 specimens revealed similar changes: myocyte hypertrophy, focal myofibrillar lysis, interstitial fibrosis, few and scattered lymphocytic infiltrates, and endocardial fibrous thickening. These features were considered consistent with the diagnosis of idiopathic dilated cardiomyopathy. In addition, foci of fibrosis and adipose tissue intermixed with hypertrophic myocytes were observed in patient 1. No cytoplasmic inclusions were recognized in myocytes or in other cells by light microscopic examination.

Numerous heterogeneous electron-dense bodies (Figure 1) were observed in most cardiac myocytes obtained from both patients. They ranged in size from 0.2 to 2.5 μm. Most were round or oval in shape but some had irregular outlines. Many morphologic patterns were observed, including bodies with a clear core surrounded by dense haloes, and bodies with lamellas surrounding an electron-dense central core. They were located as free-standing entities in the sarcoplasm, among myofibrils, within mitochondria, and sometimes were superimposed on lipid droplets. Similar inclusions were observed in the lysosomes of endothelial cells and blood granulocytes. A lipid nature to these bodies was suggested by their osmiophilia. No metallic compounds were detected on energy-dispersive x-ray microanalysis, performed with a Philips electron microscope 400T instrument.

The inclusions found in the present study are morphologically similar to those reported previously in other tissues of patients and experimental

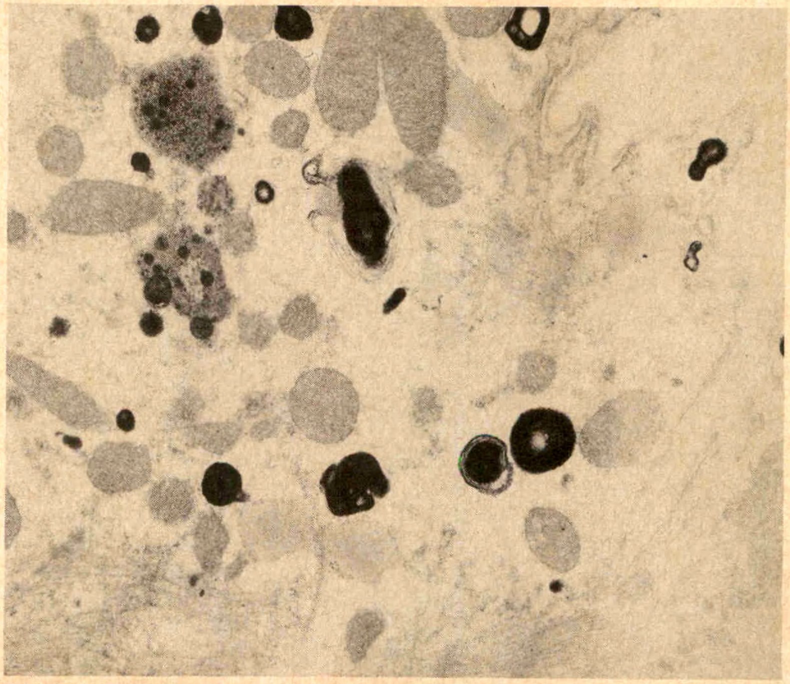

FIGURE 1. Electron micrograph of myocyte from patient 2 showing numerous electron-dense, free-standing bodies with lamellar structures in the sarcoplasm (uranyl acetate and lead citrate stain, × 23,000, reduced by 42%).

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animals given amiodarone.[1-5] The currently accepted concept of the pathogenesis of these inclusions is that they are lysosome-derived structures[3] and that the lamellas represent phospholipid materials. Amiodarone forms drug-lipid complexes that inhibit the intralysosomal degradation of phospholipids by phospholipases.[3,5] Therefore, these lamellas are regarded as a manifestation of a systemic, drug-induced, lysosomal storage disorder, best classified as a drug-induced dysphospholipidosis. These disorders can be induced by a wide variety of drugs,[3] including chloroquine,[6] which shares with amiodarone the ability to affect cardiac myocytes; however, in addition to lamellas, chloroquine also induces the formation of curvilinear bodies in cardiac myocytes.[6] These bodies are not induced by amiodarone.

Of our >300 consecutive patients with idiopathic dilated cardiomyopathy who underwent cardiac biopsy, >40% had received amiodarone treatment; among 247 biopsy specimens examined thus far by electron microscopy, only the 2 patients described herein had findings consistent with amiodarone-induced inclusions in cardiac myocytes.

Experiments in dogs show that such inclusions can be induced after only 1 week of therapy.[4] We suspect that the presence of lamellar deposits are not a simple function of the amount of amiodarone received by our 2 patients and that other, still undetermined factors may modulate the expression of this cellular abnormality, thus accounting for its infrequency among our patient population and for the lack of previous reports of these lamellas in patients receiving amiodarone. It is unclear whether these deposits are indicative of clinically significant myocardial toxicity of amiodarone.

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Intravascular Ultrasound for Diagnosis of Aortic Dissection

Abhay Pande, MD, Bernhard Meier, MD, Martin Fleisch, MD, Raoul Kammerlander, MD, François Simonet, MD, and René Lerch, MD

During the past 2 decades, advances have been made in the diagnosis of aortic dissections through computerized tomography, magnetic resonance imaging, 2-dimensional echocardiography, transesophageal echocardiography and fiberoptic angioscopy. Recently, intravascular ultrasound imaging has been added to the diagnostic armamentarium. This technique provides information on arterial wall characteristics, luminal diameter, intimal flaps, and dissections in vitro and in animal studies in vivo. It increases the sensitivity and specificity for the diagnosis and improves the delineation of the extent of aortic dissection, facilitating prompt surgical repair.[1-5] We report a case of acute aortic dissection that was diagnosed with the help of intravascular ultrasound imaging.

A 52-year-old man with longstanding systemic hypertension presented with excruciating epigastric pain and perspiration. Clinical examination revealed a heart rate of 106 beats/min with collapsing, bilaterally symmetrical pulse and no radiofemoral delay. Both carotid arteries were equally well felt. Blood pressure in the right upper arm in the supine position was 170/40 mm Hg. There were no marfanoid features. Cardiac auscultation revealed normal heart sounds, a prominent S_3 gallop, a 3/6 systolic ejection murmur and a 3/6 long diastolic murmur. The respiratory system examination was normal.

The electrocardiogram revealed sinus rhythm with ventricular premature beats, and signs of severe left ventricular hypertrophy. A chest x-ray showed mediastinal widening. Two-dimensional echocardiography with Doppler revealed prolapse of part of the right coronary cusp of the aortic valve into the left ventricle during diastole and moderate to severe aortic regurgitation. The left ventricle exhibited concentric hypertrophy and mild dilatation of the cavity. There was mild mitral regurgitation with slight left atrial enlargement. The ascending aorta was severely dilated with an intimal flap visible in the proximal part.

The patient was subjected to an intravascular ultrasound examination in conjunction with aortic angiography. The imaging system consisted of a single rotating 20-MHz ultrasound crystal mounted on the tip of a 6Fr catheter and connected to an imaging console displaying 2-dimensional images at a frame rate of 12/min (Diasonics). The catheter was introduced in a Monorail fashion, with only the distal part tracking over a 0.020-inch backup guidewire (Schneider) through an 8Fr arterial sheath with sidearm (USCI). The aortic dissection was found to originate immediately supravalvular in the ascending aorta (Figure 1A) and extend into the iliac arteries (Figure 1B). The ultrasound imaging required about 15 minutes. Aortography confirmed these findings (Figure 2). Several atherosclerotic plaques were identified in the ascending aorta by ultrasound only.

The patient underwent emergency surgical correction, consisting of transsection of the ascending aorta and replacement of the aortic valve and the ascending aorta with a valve

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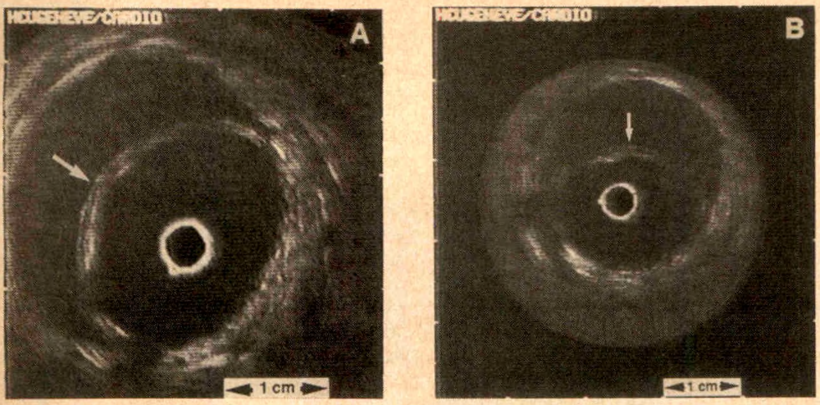

FIGURE 1. Intravascular ultrasound images of the ascending aorta *(panel A)* and the distal descending aorta immediately proximal to the bifurcation *(panel B)*. At both the levels, intimal flap *(arrows)* can be clearly identified.

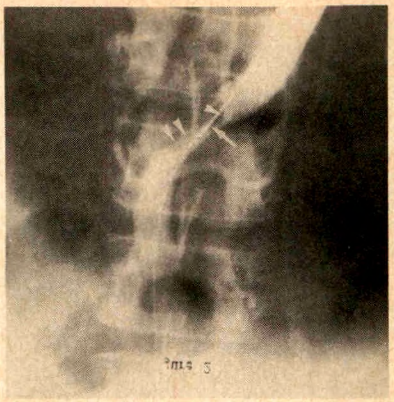

FIGURE 2. Iliac aortogram through the femoral sheath for the ultrasound catheter showing aortic dissection *(arrowheads)*. The large *arrow* points to the ultrasound catheter.

conduit tube graft by the technique described by Bentall and DeBono.[6]

The usefulness of intravascular ultrasound for the demonstration of aortic dissection has been previously documented in an experimental animal study.[1] This case, to our knowledge, represents the first report in which this technique was used for the diagnosis of acute aortic dissection in humans. With use of intravascular ultrasound, it was not only possible to localize the origin, but also to evaluate the extent of the dissection of the aorta. This was not possible with conventional echocardiography, which, in turn, revealed the involvement of the right coronary cusp. Transesophageal echocardiography is also useful in the diagnosis of aortic dissection. However, it can examine only part of the thoracic aorta. The intravascular ultrasound is capable of providing cross-sectional images of the entire aorta. However, in this patient, intravascular ultrasound provided no additional information to angiography that would have modified treatment strategy. The role of the invasive ultrasound approach needs to be defined.

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Mitral Valve Origin of Pedunculated Rhabdomyomas Causing Subaortic Stenosis

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Rhabdomyomas are by far the most common primary heart tumors in infants and children.[1] Usually they are multiple and have preference for the interventricular septum and adjacent ventricular wall.[2] In symptomatic patients, approximately 70% have an intracavitary rhabdomyoma with obstruction to blood flow in at least 1 cardiac chamber.[1,3] Left ventricular outflow obstruction by rhabdomyoma as the dominant clinical feature is extremely rare. Only 3 cases have been documented.[3-5] The present report documents another case with successful surgical resection.

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Manuscript received October 25, 1990; revised manuscript received and accepted November 20, 1990.

A 23-day-old boy was referred for evaluation. Pregnancy and delivery had been uneventful. A precordial murmur was heard shortly after birth. The baby was normally developed. Arterial pulse was normal, with normal peripheral pulsations. The first and second heart sounds were normal and a grade 2/6 ejection murmur was audible, maximally at the lower left sternal border. Electrocardiogram showed sinus rhythm with normal P waves and PR intervals. The QRS axis was +75° and the QRS complexes were normal in configuration. The chest x-ray showed a normal cardiothoracic ratio and normal lung vascular markings. Two-dimensional echocardiography revealed a lobulated and highly mobile mass in the left ventricular outflow tract (Figure 1, left). The mass protruded into the aortic valve orifice during systole. Doppler studies revealed obstruction with a peak systolic gradient of 50 mm Hg. Cardiac catheterization was not undertaken.

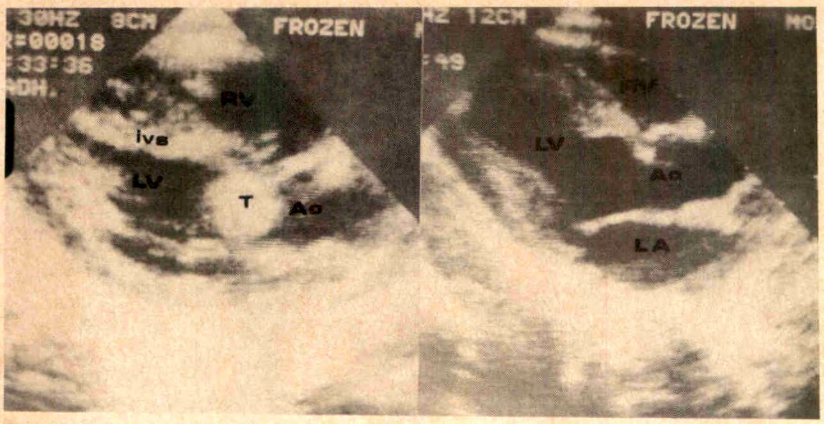

FIGURE 1. Two-dimensional echocardiograms showing a long-axis cross section of the left heart. *Left,* a tumor mass in subaortic position obstructing the left ventricular outflow tract. During systole the mass moved into the aortic orifice. *Right,* similar view, 1 year after operation. There are no residual abnormalities. Ao = aorta; ivs = interventricular septum; LA = left atrium; LV = left ventricle; RV = right ventricle; T = tumor.

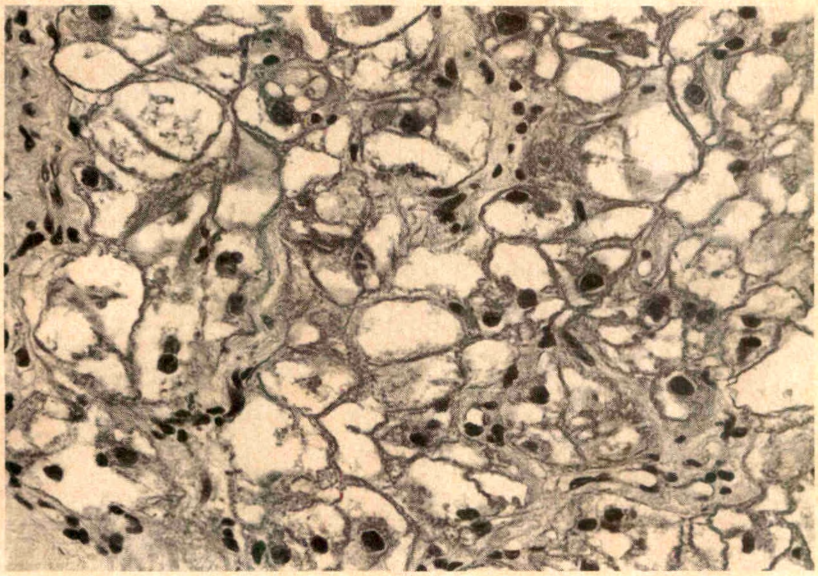

FIGURE 2. Microscopic section of one of the lesions, showing grossly swollen myocytes with features typical of rhabdomyomas (hematoxylin-eosin stain ×350, reduced by 11%).

At operation the aorta was transected at approximately 0.5 cm above the coronary orifices. Retracting the aortic valve cusps revealed 3 pedunculated globoid tumors below the aortic cusps and attached by pedicles to the ventricular aspect of the anterior mitral leaflet. Each tumor mass was estimated to measure 0.5 cm in diameter. The tumors were resected. Histologic examination showed clumps of myocytes separated from the luminal aspect by a thick layer of fibroelastic tissue. Bundles of collagen separated the heart muscle modules. The cells themselves showed an almost empty cytoplasm with accumulation of the myofilaments along the peripheral cell membrane and in strands that often connected the nucleus to the outer parts of the cell (Figure 2). Stains for glycogen were positive. At other sites the cytoplasmic changes were less outspoken and, occasionally, clumps of myocytes were present with an almost normal appearance. In one area, within the fibrous tissue, a few calcific deposits were present.

Diagnosis of rhabdomyoma was made. The patient had an uneventful postoperative recovery. At 1-year follow-up, a 2-dimensional echocardiogram (Figure 1, right) revealed a normal left ventricular outflow tract with normal functioning mitral and aortic valves. The total follow-up at the present time is 3 years and the infant is doing well.

The present case is of interest because (1) multiple small pedunculated rhabdomyomas caused subaortic stenosis as the dominant clinical feature, (2) the pedicles were attached to the ventricular aspect of the anterior mitral valve fibrous continuity, and (3) the hamartomatous nature of this lesion appears to be strengthened by the aforementioned observation.

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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

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3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

*Defined as a combination of definite coronary death and/or definite myocardial infarction. $P = .013$; 95% CI 13.3-111.5.

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